The Journal of Pediatrics

VOL. 13 NOVEMBER, 1938 NO. 5

Original Communications

INSPISSATION OF SECRETION, DILATATION OF THE DUCTS AND ACINI, ATROPHY AND FIBROSIS OF THE PANCREAS IN INFANTS

A CLINICAL NOTE

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DURING the past fifteen years examination of the pancreas in over 2,800 necropsies has disclosed thirty-five examples of a well-defined pathologic lesion, the existence of which was unsuspected during life. The patients in this series of cases, with the exception of five who died soon after birth, either failed to gain or lost in weight. Frequently episodes of diarrhea developed, and they finally died with a widespread pulmonary infection. Separate consideration will be given to seven patients who presented, in addition, wasting, especially apparent in the buttocks and thighs, distention of the abdomen, and "fatty" stools.

The lesion of the pancreas here under consideration was observed and its importance recognized by S. B. Wolbach many years ago. At necropsy, on gross examination, the transverse diameter of the pancreas is decreased. The organ is extremely firm in consistency so that considerable resistance to cutting is encountered. Microscopic examination reveals severe distortion of the architecture (Fig. 1). The acini and small ducts are greatly dilated, and their lining epithelium is flattened or occasionally obliterated. The lumina are filled with inspissated material laid down either in concentric rings or in homogenous masses. Extensive fibrosis is found. In many areas small islands of dilated acini and small ducts, separated from each other by delicate connective tissue, are surrounded by large amounts of coarse fibrous tissue. Atrophy of acini and ducts and replacement of large portions of the exocrine tissue of the pancreas by fibrous tissue marks the most advanced stage

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of the process (Fig. 2). Lymphoid and leucocytic infiltration of the interstitial tissue is often, but not always, present. The islet tissue does not partake actively in the pathologic process. No evidence of congenital anomalies or gross obstruction of the ducts could be found in those instances where it was possible to examine completely the duct system. In addition to the thirty-five patients with such advanced lesions in the pancreas, early stages of the process have been encountered in over two hundred patients at necropsy. Slight fibrosis is frequently encountered. The early changes are not recognizable on gross examination but microscopically there is dilatation of acini which contain inspissated secretion.

From a study of the development of the lesion in the large amount of material available, Blackfan and Wolbach, in 1933,[1] offered a provisional explanation in regard to pathogenesis. They stated, "Our preliminary studies indicate that the pathogenesis of this striking pancreatic affection resides in the production of an abnormal secretion which inspissates and leads to distention and atrophy of ducts and acini."

The lungs showed changes characteristic of the usual type of chronic pneumonia in infants and children. This type of pneumonia is primarily an interstitial one with secondary involvement of the alveoli and alveolar ducts. Characteristically the bronchioles and small bronchi are greatly dilated. Their walls are thickened and surrounded by collections of large mononuclear cells and lymphocytes. The dilated lumina of the bronchioles are filled with collections of polymorphonuclear cells. Frequently destruction of the walls of the bronchioles is encountered. Widespread replacement of lung parenchyma by connective tissue, and scattered manifestations of regeneration of alveolar epithelium are found in the more chronic examples of the condition.

The histologic change characteristic of vitamin A deficiency, namely metaplasia of lining epithelium in various parts of the body (trachea, bronchi, renal pelvis, or pancreas) to a stratified squamous type, was found in seven of the patients at necropsy.

From an analysis of the records of this series of patients it was found that the clinical manifestations begin very early in life. Five infants died within the first few days of life. In the remaining thirty patients the early signs of a disorder of nutrition developed before they were one year of age, the average age of onset of symptoms being about two months.

As to the family history, one patient was born of a mother who had an "intolerance" for fats and on this account had eliminated "fats" from her diet. The twin of this infant who died at another hospital is not included in this series, but both of these infants presented at necropsy histologic changes of vitamin A deficiency in addition to the pancreatic lesion. Another example of multiple occurrence in a family

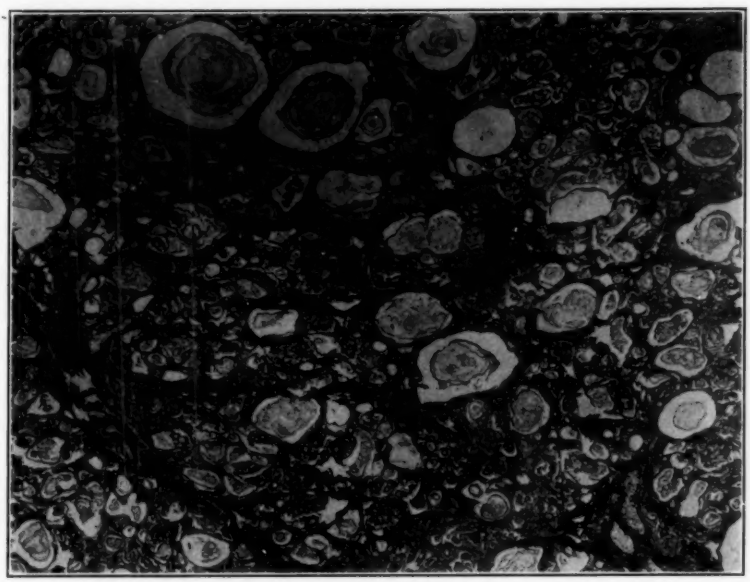

Fig. 1.—Pancreas of patient in Case A-34-21. (×33—aniline blue.) Symptoms from birth. Weight 12 pounds at 1 year of age. Developed "celiac disease" syndrome. Died at 2 years of age weighing 10 pounds. Chronic pulmonary infiltration was present but no pathologic evidence of vitamin A deficiency.

Fig. 2.—Pancreas of patient in Case A-34-21. (×233—aniline blue.) Detail of same section of pancreas shown in Fig. 1.

is that of twins who died a few days after birth. Both of these infants showed at necropsy a lesion of the pancreas as well as intestinal stenosis and meconium ileus. Mild episodes of vomiting, pyelitis, or eclamptic symptoms were reported during pregnancy by seven mothers. The mother's diet during pregnancy was restricted in only one case, that mentioned above where the "intolerance" for fats was claimed. In all but two cases, the infants were born at term by normal delivery.

Eighteen of the patients were breast-fed for from one to thirty-two weeks, the average being eight weeks. Those artificially fed were given modifications of cow's milk. The fat was markedly reduced in the food of five patients. Fifteen patients who lived more than one month had not received cod liver oil or vitamin A concentrates. Some infections, such as conjunctivitis, pyodermia, pyelitis, or frequent upper respiratory infections were conspicuous in the past history of twenty-five patients. So far as we were able to determine, there were no other specific incidents in the family or past history which might have a bearing on the production of the symptoms or the underlying associated lesion in the pancreas.

The clinical manifestations were limited in variety but were so common to many disorders in infancy that it has not been possible to determine accurately the dependable diagnostic features. However, there was an apparent uniformity in the onset and course of the illness which may be summarized as follows: In the usual course of events the patients developed symptoms of illness referable either to the gastrointestinal system or the respiratory system. In many instances such signs of ill health as vomiting and diarrhea, with failure to gain or loss of weight preceded the onset of signs of infection of the respiratory system, but in other instances a pronounced and unproductive cough was an early complaint. Sooner or later a productive cough and physical signs of pulmonary infiltration made their appearance. Vomiting as a rule was neither persistent nor frequent. Diarrhea was more significant, occasionally being severe, and often present for prolonged periods. The stools did not show pus or blood. The appearance of "fatty" stools was not observed except in seven patients who will be mentioned later.

With the persistence of these symptoms and with continuing loss of weight, the appearance of the infants was that of extreme emaciation with the attendant signs of a disorder of nutrition with or without the physical findings indicative of bronchopneumonia. Fever and dehydration did not become outstanding features until relatively late in the course of the illness. Roentgenograms showed generalized infiltration of the lungs in twenty-four patients. The tuberculin test and the Hinton test were negative.

The average duration of illness for the thirty patients who lived beyond the neonatal period was six months, and their average age at death was eight months. Several infants lived a year or more after the appearance of symptoms, but all died before the age of two years. The other five infants died, as mentioned above, within three weeks of birth—three of them with intestinal stenosis and meconium ileus, one with atresia of the ileum, and the other infant with cirrhosis of the liver.*

Fig. 3.—M.C. (Case 1, Table I.) at the age of 22 months. Died at 2 years.

Let us now consider the seven patients who presented such clinical features as emaciation, distention of the abdomen, and large, pale, putrefactive, "fatty" stools. While in general their illness and course were uniform with those of the other patients who lived beyond the

*Pathological examination revealed no evidence of defect in the biliary system. The bile capillaries were distended with bile and the liver cells laden with pigment. Small foci of necrosis were found in the portal areas, and a definite but slight increase in connective tissue was evident throughout the liver. The pathogenesis of the changes in the liver was obscure.

neonatal period, they stand out because in addition they developed these signs usually providing the basis for a tentative diagnosis of "celiac disease" (Fig. 3).

The ages of these seven patients at the onset of their symptoms were scattered from birth to one year. However, in this group the average duration of symptoms was sixteen months, which is much longer than the average of six months for the entire series of thirty patients who lived beyond the neonatal period. Thus their average age at death was twenty months in contrast to the average of eight months for the group of thirty patients.

While seven patients developed clinical symptoms suggesting "celiac disease," adequate data to determine the presence of all of the features of this syndrome* were obtained in only two patients because of limitations imposed by brief periods of observation or the severe illness of the patient. The clinical and laboratory data of these two patients whose symptoms dated from birth and continued with exacerbations and remissions until death occurred at twenty-four and thirteen months, respectively, are presented in Table I.

TABLE I

	CASE 1 M. C.	CASE 2 N. D.
Wasting	+	+
Abdomen	Distention	Distention
Diarrhea	+	+
Stools	"Fatty"	"Fatty"
Vomiting	0	0
Gastrointestinal roentgenograms	Clumping	Clumping
Chronic bronchopneumonia	+	+
Glucose tolerance curve	Flat	Flat
Stool analysis—Fat (% dry wt.)	58%	41%
Blood	Secondary anemia	Secondary anemia

It has been pointed out in this group of seven patients that the symptoms had existed for a much longer period than was true of the majority of the infants. That the "celiac disease" syndrome should develop when such severe lesions in the pancreas had existed so long is not too surprising, as similar manifestations have been reported in association with loss of pancreatic tissue in humans[4, 5] and in experimental animals.[6]

As to the occurrence of definite evidence of vitamin A deficiency on pathologic examination in seven of the patients in the entire series of thirty-five cases, it would be expected that any interference with the

*Until recently we have considered the "celiac disease" syndrome as including the characteristic wasting, distention of the abdomen, large, pale, putrefactive, "fatty" stools, excess fat in the feces by chemical analysis, clumping of barium in the small intestine, and "flat" glucose tolerance curve.

As mentioned by Fanconi,[3] Schiff,[3] and others, and as we have observed repeatedly, the features of the "celiac disease" syndrome may appear as a result of a variety of disorders which interfere with the proper utilization of food substances, particularly fat. Thus it would seem unwise to take these criteria as pathognomonic signs of a particular disease.

absorption of fat as a result of this lesion in the pancreas might affect the absorption of fat-soluble vitamin A.

Vitamin A absorption tests* were performed in the two patients whose clinical and laboratory data are summarized in Table I. When a single large dose of oleum percomorphum was given orally, the level of vitamin A in the blood did not rise during the following twenty-four hours as it usually does in normal children. But when thirty drops of oleum percomorphum were given daily, the vitamin A gradually rose to a normal level. After death the liver tissue was found to contain an abundance of vitamin A. The inference may be drawn that although vitamin A could be absorbed, the efficiency of absorption was probably diminished.

In the group of seven patients whose illness was of long duration and who finally developed the "celiac disease" syndrome, the only one who revealed pathologic evidence of vitamin A deficiency had not received accessory vitamin A in the diet. It is interesting to note that five of the total of seven patients who showed histologic evidences of vitamin A deficiency had not received accessory vitamin A in their diet. One may presume that the requirements of vitamin A for these patients may well have been greater than usual because of diminished absorption and infections. However, this should not be construed as indicating that vitamin A deficiency plays an important part in the production of the lesion, as we have seen an even greater number of patients with vitamin A deficiency in whom the pancreas was normal in every respect.

The clinical and laboratory manifestations herein reported together with so characteristic a lesion in the pancreas (dilatation of ducts, etc.) are similar in many respects to reports which have appeared in the literature for many years.[9-14] That an interrelationship exists between them certainly must be entertained, but further studies are needed before a clear understanding of any such interrelationship can be established.

While the possibility of a lesion of the pancreas should be considered in infants presenting the clinical and laboratory features which have been outlined, it is apparent that before a definite diagnosis can be established, investigation of the exocrine function of the pancreas will be needed. This would consist of indirect estimation through "balance" studies of fat and nitrogen absorption,[15] or direct estimation of the concentration of the pancreatic enzymes in the duodenum.[16]

SUMMARY

A note is presented on the clinical manifestations of thirty-five infants in whom an advanced lesion of the pancreas was found at necropsy. The

*Vitamin A analyses were performed by techniques based on those of Clausen[7] and Chesney and McCoord.[8]

lesion is characterized by inspissation of secretion, dilatation of the ducts and acini, atrophy and fibrosis. The need for further information concerning the absorption of fat and especially nitrogen, as well as pancreatic enzymes, as an aid to diagnosis, is suggested.

We are indebted to Dr. S. B. Wolbach and Dr. Sidney Farber for their assistance in describing the pathology of the pancreas and in the preparation of this communication.

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THE CAROTINOIDS AND VITAMIN A OF THE BLOOD

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THE proof that carotene is converted into vitamin A by the body[1] suggested that a study of the concentration of the carotinoid pigments and of vitamin A in the blood might be profitable. Such a study is obviously necessary for the elucidation of the problem of the intermediary metabolism of these substances. In this paper we shall call attention to the more important factors which affect the blood content of the carotinoids and of vitamin A, i.e., placental transmission, diet, infection, age and season, and we shall discuss the effect of chronic morbid states—diabetes, Bright's disease, celiac disease and hypothyroidism—on the concentration of carotinoids and vitamin A in the blood.

The carotinoid pigments are derived from plants and include isomeric carotenes ($C_{40}H_{56}$), of which those containing a β-ionone ring may serve as precursors of vitamin A, unsaturated hydrocarbons without rings of the same empirical formula (such as lycopin, the pigment of the tomato), and carotinoids containing oxygen, such as the xanthophylls, the function of which in the animal is not yet apparent.

The blood and tissues of man may contain appreciable amounts of several of these pigments.[2] So far as we know, the "lipochromes," or yellow fat-soluble pigments are carotinoids, possibly exclusively so.

METHODS

Since the blood cells contain little, if any, carotinoid, the analyses here reported have been made upon serum or plasma. For total carotinoids we have used a modification of the method of Connor.[3]

Method for Determining Total Carotinoids.—Three milliliters of plasma or serum are mixed with an equal volume of 95 per cent ethyl alcohol; 3 ml. of petroleum ether are added. The mixture is shaken at intervals for ten minutes and is centrifuged. The upper layer, containing all the carotinoids (and the vitamin A), is compared in the micro-Duboseq colorimeter with a standard of 0.02 per cent aqueous solution of potassium bichromate. The standard is prepared by dilution of a 0.2 per cent solution which keeps well for months. When the upper layer has exactly the same intensity of color as the dilute standard, the original plasma is said to contain 100 units of carotinoid per 100 ml. We have found that when solutions of pure carotene or xanthophyll are used, the relationship between colorimeter readings and concentration is linear

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over a very considerable range. One hundred units of carotene are equal to 137 micrograms (γ); 100 units of xanthophyll are equal to 146 γ.

Method for Determining Carotene and Xanthophyll.—For carotene and xanthophyll analyses, we have used the method described by Clausen and McCoord.[4] We are aware of the fact that this method may give high results for carotene because lycopene and the esters of xanthophyll may be included with it; also, the results for xanthophyll may be low (*l.c.*). But the more important conclusions of the present study are not influenced by these facts because the factors investigated affect the carotene and the xanthophyll in a like manner.

Method for Determining Vitamin A.—The vitamin A content of the plasma (or serum) was estimated by a modification of the Price-Carr antimony trichloride reaction.[5] One milliliter of the petroleum ether extract of plasma already described is evaporated to dryness in a small test tube. One-tenth milliliter of chloroform is added; then 1 ml. of a 30 per cent solution of antimony trichloride in chloroform is added, and the mixture is rapidly transferred to the cup of the micro-Dubosecq colorimeter with the plunger set at 10 mm. The other cup of the colorimeter contains an aqueous solution of 10 per cent copper sulfate ($CuSO_4 \cdot 5\,H_2O$). The comparison of the blue colors must be made within 30 seconds after mixing. When the color of the solution containing vitamin A is exactly matched by 10 mm. of copper sulfate, the original specimen is said to contain 100 units of vitamin A per 100 ml. Corrections are made for the carotene and xanthophyll content of the plasma by subtracting 3.7 blue units for each 100 γ carotene, and 4.1 blue units for each 100 γ xanthophyll or 2.7 blue units for each 100 units total carotinoid. Details will be published later. In many cases the analyses for total carotinoids *or* for carotene and xanthophyll were carried out on the same specimen as was the analysis for vitamin A. We are aware of the error which we tacitly make in identifying the "units" of blue color with "units of vitamin A" but feel that the average results to be presented may be a fairly accurate measure of vitamin A concentration.

CLINICAL MATERIAL

Early in this investigation it became evident that the concentration of carotinoid pigments and of vitamin A in the plasma varied considerably. A marked and prompt decrease in concentration accompanied infection and was proportional to the duration and severity of the infection. Consequently, some arbitrary classification of infections in the persons observed was necessary. We have considered as "severe" infections pneumonia, mastoiditis, meningitis, septicemia, and any fatal infection. All others were considered "mild or moderate" infections.

Since the carotinoid pigments of the blood are exogenous so far as we know and may enter the body through the placental circulation or from the food (colostrum, milk during the first few months, and pigmented vegetables later), we have presented separately the results of analysis (1) at birth, (2) in children under 6 months of age, (3) in those from 6 months to 24 months of age, and (4) in persons over 2 years of age. Each of these four age groups is divided into three subgroups: (a) those with no infection, those (b) with mild or moderate infection, and (c) those with severe infection. We have separated from all these groups for special consideration those metabolic disorders found to have a marked effect upon the level of plasma carotinoids and vitamin A—diabetes, Bright's disease, celiac disease, and hypothyroidism and hyperthyroidism. If the mean values in any group are to be of statistical significance, the groups must be fairly large, because the coefficients of variability are large. In several of the tables will be found the number of observations, the mean, the standard deviation (σ) and the probable error of the mean (P. E. M.). As a rule, the frequency distributions of the values are not normal, the mode being considerably below the mean. This is apparent in Tables V and VIII.

NEWBORN INFANTS AND THEIR MOTHERS

Blood was obtained from the umbilical artery and vein of the infant and from the mother's vein at delivery. The results of individual analyses permit the calculation of various correlations, as well as the calculation of means and standard deviations, which are presented in Table I. In a preliminary discussion of these results,[9] we have presented evidence that we are dealing with carotene and xanthophyll. If Table I is compared with Table III, containing the results in normal older children and adults, it will be evident that (1) the carotinoid pigments of the plasma at birth are lower than in later life, (2) the xanthophyll concentration at birth exceeds that of carotene, the reverse being true later, (3) vitamin A is relatively low in the blood at birth, and (4) the concentration of carotene and xanthophyll in the blood of parturient women is higher on the average than it is in other older persons. Table I also shows that the mean value of concentration of carotene and xanthophyll is significantly higher in the venous blood (that from the placenta) than it is in the arterial blood (that from the child). When the venous and arterial blood of the *same* individual were compared, it was found that the concentrations in the venous blood exceeds that in the arterial blood in *every case* (Table II). This fact is strong evidence that the carotinoids are passing by way of the placenta to the fetus at the time of birth. A very rough estimate shows that about 1 mg. of carotene per kilogram of fetus per day might be furnished to it in this way, provided the rate of transfer during life in utero is the same as that at

TABLE I*

CAROTINOID AND VITAMIN A OF FETAL AND MATERNAL BLOOD PLASMA AT BIRTH

	NUMBER	MEAN	σ	P.E.M.
Carotene				
Infant venous blood	63	16.60	5.73	0.49
Infant arterial blood	38	12.90	4.70	0.53
Maternal venous blood	32	114.0	40.6	4.94
Xanthophyll				
Infant venous blood	63	27.8	9.07	0.78
Infant arterial blood	38	21.3	8.20	0.91
Maternal venous blood	31	83.7	26.6	3.23
Vitamin A				
Infant venous blood	63	12.8	4.78	0.41
Infant arterial blood	37	13.1	4.80	0.54
Maternal venous blood	32	15.2	6.49	0.79

*In the tables, *N* designates number of observations; *M*, means; σ, standard deviation; *P.E.M.*, probable error of mean; *C*, carotene, γ per 100 ml.; *X*, xanthophyll, γ per 100 ml.; *Total C*, total carotinoid, units per 100 ml.; *A*, vitamin A, units per 100 ml.

TABLE II

DIFFERENCES BETWEEN CONCENTRATION OF CAROTINOIDS IN VENOUS AND IN ARTERIAL BLOOD OF THE NEWBORN CHILD

	NUMBER	MEAN	σ
Carotene	36	6.7	2.7
Xanthophyll	34	7.2	6.9

TABLE III

CAROTENE, XANTHOPHYLL AND VITAMIN A OF PLASMA AT VARIOUS AGES (INFLUENCE OF INFECTION)

	INFECTIONS								
	NONE			MILD OR MODERATE			SEVERE		
	N	M	σ	N	M	σ	N	M	σ
Carotene									
Birth	63	16.60	5.73	–	–	–	–	–	–
0-6 mo.	5	25.5	–	1	49.5	–	1	9.5	–
6-24 mo.	3	76.2	–	23	71.6	55.7	7	40.9	–
2 yr. +	108	94.1	42.6	61	70.8	32.6	19	50.6	7.25
Xanthophyll									
Birth	63	27.8	9.07	–	–	–	–	–	–
0-6 mo.	5	29.5	–	1	49.5	–	1	29.5	–
6-24 mo.	3	29.5	–	23	38.2	24.8	7	23.8	–
2 yr. +	108	53.0	25.2	61	38.4	16.4	19	37.9	15.0
Vitamin A									
Birth	63	12.8	4.78	–	–	–	–	–	–
0-6 mo.	14	23.8	10.7	20	15.0	7.1	14	9.1	5.2
6-24 mo.	12	19.9	5.2	75	12.9	7.05	24	9.5	6.9
2 yr. +	116	20.2	10.0	144	15.1	8.2	67	6.8	5.5

birth. The mean concentration of vitamin A in the venous blood plasma of the fetus is about equal to that in the arterial blood plasma. The variations in individual cases were found to take place in both directions. This may be due to errors of analysis, or, assuming that the analyses are correct, may be due to transfer of vitamin A by way of the placenta in some of the cases.

CAROTINOIDS AND VITAMIN A OF PLASMA AFTER BIRTH

The mean values for carotene, xanthophyll, and vitamin A are shown in Table III. In persons without infection the values for carotene rise after the sixth month, when, as a rule, green vegetables and carrots are added to the diet. The rise in xanthophyll occurs at about the second year. Vitamin A rises soon after birth to an approximately constant average level of about 20 units per 100 ml. Severe infections are accompanied by a marked fall in carotene and in vitamin A; after the second year, also by a fall in xanthophyll.

The mean value for vitamin A of the plasma in childhood does not vary greatly at different seasons of the year (Table IV), whereas in normal older children the plasma carotinoids are higher in the late summer (Table VII).

The distribution of values for vitamin A in the plasma in the group studied is very asymmetrical about the mean (Table V). For example, the vitamin A of plasma in normal persons most frequently lies between 10 and 20 units per 100 ml., whereas the mean is 20.5 units. For this reason, too much significance must not be placed upon a single low result. Either a series of analyses must be made upon one individual under controlled conditions, or the mean and the probable error of the mean must be determined in a sufficient number of different individuals

TABLE IV

SEASONAL VARIATIONS IN VITAMIN A OF PLASMA

MONTHS	INFECTIONS					
	NONE		MILD OR MODERATE		SEVERE	
	N	M	N	M	N	M
December, January, February	35	21.9	112	13.2	45	8.1
March, April, May	33	22.8	60	14.9	33	7.5
June, July, August	71	18.7	52	15.9	19	7.5
September, October, November	3	23.7	15	15.3	8	7.6

TABLE V

VITAMIN A OF PLASMA

UNITS A PER 100 ML.	INFECTIONS		
	NONE	MILD OR MODERATE	SEVERE
0- 4	2	13	29
5- 9	18	69	46
10-14	32	53	17
15-19	30	48	12
20-24	14	28	1
25-29	20	14	
30-34	6	10	
35-39	7	2	
40-44	4	2	
45-49	9		
N	142	239	105
M	20.5	14.4	7.72
σ	11.3	8.1	4.90

in whom one known factor is abnormal, and in whom the other variable factors do not affect the level of vitamin A.

A correlation exists between the levels of carotene and xanthophyll of the plasma. Considering only persons over 2 years of age, without infection, and without metabolic diseases which affect the levels of plasma carotinoids, we have estimated the coefficient of correlation and have calculated the mean, standard deviation and regression lines for 450 pairs of observations.

Coefficient of correlation	$r = 0.816$
Mean carotene concentration	$c = 90.52\ \gamma$ per 100 ml.; $\sigma = 45.3$
Mean xanthophyll concentration	$x = 53.9\ \gamma$ per 100 ml.; $\sigma = 28.7$

$$c = 1.29\ x + 2.07$$
$$x = 0.394\ c + 18.2$$

It follows that for certain statistical purposes, the total carotinoids may be used instead of carotene and xanthophyll. The high coefficient of correlation undoubtedly is due to the fact that the carotene and xanthophyll contents of the average diet are correlated.

TOTAL CAROTINOIDS OF THE PLASMA IN CHILDHOOD

The chief factors which affect the plasma concentration of carotinoids are the intake, infection, and certain metabolic disturbances.

The Effect of Intake.—It has been shown[6] that the level of plasma carotinoid rises slowly in young infants who are fed carrot puree, or solutions of carotene in oil, and that the presence of infection may interfere with the rise in level. If a large single dose (20 ml. 0.3 per cent carotene in oil) is administered to normal children, the increase in level appears to be influenced to some extent by the original level present (Table VI). With original levels below 150 units per 100 ml., a slow rise occurs which reaches a maximum in three days, and which is still apparent after seven days. With original levels above 150 units, the rise is greater, and the maximum is reached in twenty-four hours. The rate of absorption of carotene appears to be slower than the rate of absorption of vitamin A, for, when large doses of halibut liver oil are given, the maximum concentration of vitamin A in the plasma is found four hours afterwards.[6]

TABLE VI

MEAN INCREASE IN LEVEL OF PLASMA CAROTINOIDS FOLLOWING ADMINISTRATION OF SINGLE DOSE OF 20 ML. 0.3 PER CENT CAROTENE IN OIL

GROUP I—ORIGINAL PLASMA LEVEL BELOW 150 UNITS PER 100 ML.
GROUP II—ORIGINAL PLASMA LEVEL OVER 150 UNITS PER 100 ML.

(TEN OBSERVATIONS IN EACH GROUP)

	TIME UNITS PER 100 ML.								
	3 HR.	5 HR.	10 HR.	24 HR.	30 HR.	48 HR.	72 HR.	92 HR.	1 WK.
Group I	6.8	8.2	17.0	37.8	41.8	43.2	48.0	41.8	25.6
Group II	20.6	37.4	50.8	53.2	28.2	29.2	40.7	56.6	41.2

The average level of plasma carotinoids rises from about 20 units per 100 ml. at birth to about 100 units at 18 months, and falls to a constant level of about 90 units by the fifth year. The average level during the winter months is about 77; in late autumn about 100 (Table VII). These observations are readily explained by the varying intake of carotinoids which is low until infants receive vegetables, and which is lower in mid-winter than in the spring and summer. When the intake of carotinoids is diminished by giving a diet free of pigmented vegetables, eggs, butter, and cream, the level of plasma carotinoids falls gradually from about 100 units to about 50 units in the course of a week (Fig. 1).

Correlation of Total Carotinoids With Vitamin A of Plasma.—Since both the carotinoids and vitamin A of the plasma fall during infection,

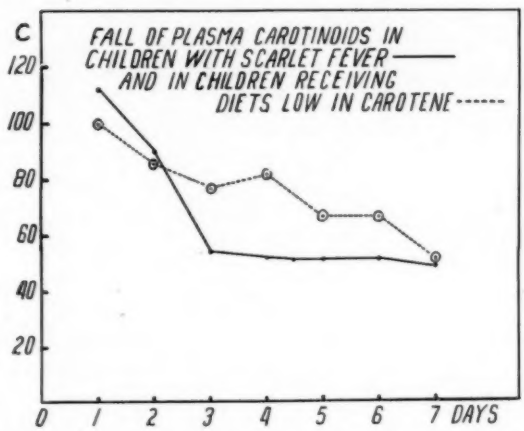

Fig. 1.—The fall in carotinoids of the plasma of children receiving diets low in carotinoids is gradual. The fall in carotinoids of the plasma of children with moderately severe scarlet fever is rapid.

it would seem natural to suppose that a correlation should exist between those substances in a large group of persons. In 1,414 pairs of observations we found that the coefficient of correlation was +0.305. When,

TABLE VII

SEASONAL VARIATION OF PLASMA CAROTINOIDS IN PERSONS OVER 2 YEARS OF AGE

MONTHS	INFECTIONS					
	NONE		MILD OR MODERATE		SEVERE	
	N	M	N	M	N	M
December, January, February	187	77.2	157	70.0	37	36.6
March, April, May	241	93.3	189	69.7	35	38.7
June, July, August	213	90.7	103	69.1	8	40.0
September, October, November	306	109.5	58	73.4	19	35.9

however, the groups were divided into subgroups (1) with no infection, (2) mild or moderate infection, and (3) severe infection; we found in the subgroups very low coefficients of correlation.

Correlation of Total Carotinoids With the Lipids of the Plasma.—In 84 children convalescent from rheumatic fever or from scarlet fever, the coefficient of correlation between total carotinoids and phospholipids or residual fat was too small to be of significance. The coefficient of correlation between total carotinoids and total cholesterol was +0.585.

The Effect of Infection.—The fall in level of plasma carotinoids during infection is also illustrated in Fig. 1 which shows that in 11 cases of mild scarlet fever the fall in plasma carotinoids to a low nearly constant level (about 50 units) may take place in 3 days. The frequency with which various levels of carotinoids are found in the plasma of children with no infections, mild or moderate infections, and severe infections, is shown in Table VIII. It will be observed that the distributions are not symmetrical about their means but that there is a marked tendency for the occurrence of instances with higher values than the mode, especially in persons without severe infection. The variability

TABLE VIII

FREQUENCY OF VARIOUS LEVELS OF THE CAROTINOIDS OF THE PLASMA IN CHILDREN OVER 2 YEARS OF AGE

UNITS PER 100 ML. PLASMA	INFECTIONS					
	NONE		MILD OR MODERATE		SEVERE	
	CASES	PER CENT	CASES	PER CENT	CASES	PER CENT
250-259	2	0.21	1	0.17		
240-249	1	0.11	0			
230-239	1	0.11	0			
220-229	2	0.21	0			
210-219	2	0.21	1	0.17		
200-209	7	0.74	3	0.52		
190-199	5	0.53	0			
180-189	11	1.16	4	0.69		
170-179	10	1.05	0			
160-169	12	1.27	3	0.52		
150-159	23	2.43	1	0.17		
140-149	27	2.85	2	0.34		
130-139	36	3.80	6	1.03		
120-129	45	4.75	20	3.43		
110-119	59	6.24	23	3.97		
100-109	69	7.28	26	4.46		
90-99	112	11.80	39	6.69		
80-89	123	13.00	57	9.78	1	0.95
70-79	124	13.10	69	11.80	0	
60-69	116	12.20	91	15.60	5	4.72
50-59	78	8.23	102	17.50	12	11.30
40-49	56	5.91	82	14.10	27	25.30
30-39	20	2.12	42	7.21	29	27.40
20-29	4	0.42	7	1.20	21	19.80
10-19	2	0.21	4	0.69	8	7.54
0-9					3	2.83
N	947.0		583		106	
M	91.9		71.7		46.9	
σ	37.2		31.3		14.4	

TABLE IX

EFFECT OF ARTIFICIAL HYPERTHERMIA UPON VITAMIN A, CAROTENE AND XANTHOPHYLL OF PLASMA

DURATION HOURS	VITAMIN A UNITS PER 100 ML.						
	BEFORE TREATMENT	AFTER BEGINNING TREATMENT					
		IMMEDIATELY	1 DAY	2 DAYS	3 DAYS	4 DAYS	5 DAYS	7 DAYS
10	----	2.3	7.0	8.4	5.0	6.0		
14	7.1	5.0	17.6	13.8	12.0	11.4		
16	8.5	6.0						
15	8.6	5.8	15.6	18.2	22.8			13.6
16	10.8	3.5	4.5	4.7	13.5			
13	11.6	5.5	7.4	20.6	7.0			
19	12.4	3.4	7.4	7.4				
15	12.8	5.4	7.2	6.0	4.8			
16	13.6	19.8	29.3					
10	14.0	8.3	8.5	12.5	10.4	11.6		
14	16.0	9.2						
16	16.4	6.0			7.5		7.0	10.0
5	18.8	6.5	18.8					
16	25.0	14.0						
10	25.4	12.2	25.5					10.0
5	25.5	26.8	28.6	29.6				
16	26.2	7.8						
16	27.0	16.2						
14	41.5	13.5	9.4	20.5	33.5			
Mean decrement of carotene γ per 100 ml.		8.2	9.9	9.0	14.0	12.0		19.0
Mean decrement of xanthophyll γ per 100 ml.		15.0	8.7	13.0	13.0	11.0	6.0	-8.5

is considerable, as is shown by the large relative values of the standard deviations in all the distributions.

The fall in plasma carotinoids during infection is in part due to lowered intake, as already suggested by the effect of feeding diets low in carotinoid. But this effect does not account for the more rapid fall during infection. Another cause is fever. Through the kindness of Dr. Stafford Warren we have had the opportunity to observe the effect of artificial hyperthermia upon the carotene, xanthophyll, and vitamin A contents of the plasma. The results are shown in Table IX. The rapid fall in all three substances is apparent.

The concentrations of carotene and of xanthophyll fell in all cases for three days (on the average). At this time the patients resumed their normal diets. By the end of a week the xanthophyll content of the blood had risen above the initial value. The results of the analysis for vitamin A are given in detail. A marked fall occurred in 17 of the 19 persons examined; a rise occurred in 2, one of whom had had only a brief treatment. The fall is most evident as a rule immediately at the end of the treatment, and the lowest levels are found in the persons having the lowest initial levels of vitamin A. In 6 instances, the level of vitamin A increased above the initial level between the first and third day after beginning the treatment. A similar rise in the level of vita-

min A of the plasma was observed after the fall of temperature in scarlet fever (Fig. 2) and in pneumonia. The rise after fever suggests either liberation from stores, increased ingestion due to improved appetite, or temporary inability to store the vitamin as rapidly as normally. It is obvious from the observations recorded here that the finding of a low level of vitamin A in the blood during infection does not necessarily indicate low stores. It may, however, explain the occurrence of loss of visual acuity in dim light during prolonged fevers in persons with possibly normal stores of vitamin A. The decrease in plasma carotene, xanthophyll, and vitamin A during artificial hyperthermia is evidence that the low values found in infections result in part from fever.

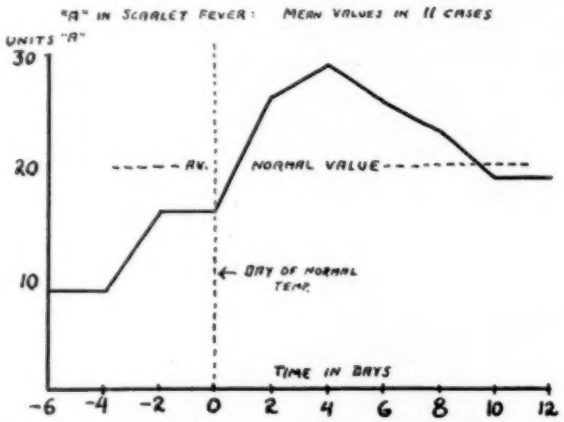

Fig. 2.—Rise in vitamin A of plasma after temperature became normal in scarlet fever reached a maximum in four days.

CAROTENE AND VITAMIN A IN DISORDERS OF METABOLISM

Xanthosis Cutis (Table X).—This name has been selected to describe those cases in which yellow discoloration of the skin is due to carotene or to xanthophyll. The term "carotinemia" is not appropriate, for two reasons: (1) The color may be due to xanthophyll; (2) the degree of pigmentation is not necessarily proportional to the concentration of carotene in the plasma. For example, no discoloration of the skin may occur in nephrosis or chronic nephritis even when the plasma contains a much higher concentration of carotinoid pigments than are found in xanthosis cutis. The condition is characterized by yellowness of the skin of the whole body, especially marked in the ears, the nasolabial folds, the palms, and the soles. The sclerae and the urine are normal. The condition has often been confused with jaundice. It need not be pathologic. It is frequently due to the ingestion of large quantities of vegetables containing carotinoids, or of eggs containing xanthophyll, and

may be produced readily in many healthy persons by such diets. It is frequently observed in diabetics, often as a result of diet, sometimes as a result of the disease as well. Several of our patients had symptoms of hypothyroidism. Two of the subjects were suspected of having Addison's disease and may, in fact, have suffered from it, as they were asthenic and had hypotension. The plasma of one diabetic patient showed normal carotene but high xanthophyll. In another (a normal child) xanthosis cutis was produced by a diet rich in egg yolk. Our observations indicate that xanthosis cutis may be apparent, without Bright's disease, when the blood carotene or xanthophyll exceeds about

TABLE X

XANTHOSIS CUTIS

HOSPITAL NO. OR INITIALS	C	X	A	TOTAL C	REMARKS
62848			63	224	Recovering from xanthosis cutis
85103	640	112			Abnormal craving for carrots, raw or cooked
None	271	76			Took large amounts of carotene in oil; slight xanthosis
86814	183	35			Recovering; skin still yellow
28444	206	30			Addison's disease
I. McC.	346	231			Diabetic; diet mostly vegetables
I. McC.	364	340			Same patient, 15 months later; same condition
97552	170	328			Diabetes; arteriosclerosis
54371	416	232	80		Marked yellowness of skin
54371	258	124			Two months later; skin somewhat less yellow
44553		.		216	Moderately yellow skin; fever
Priv. pt.	316	135			Fond of vegetables; marked xanthosis
Priv. pt.	304	168	4.6		Fond of vegetables; marked xanthosis
143917	320	110	9.4		Fond of vegetables; marked xanthosis

250 micrograms per cent, or when the total carotinoids exceeds about 200 units per cent. Xanthosis may disappear within two weeks when the diet contains little carotinoid. The pigmentation of the skin, however, may persist for some time after the level of plasma carotinoids has become normal.

Diabetes (Table XI).—The carotene and xanthophyll content of the plasma was determined in 64 diabetics, mostly adults, whose disease was under good control. Those cases requiring more than 10 units of insulin per day were considered moderate or severe. Those patients receiving less than 10 units of insulin per day were considered as having mild cases. The cases with infection at the time of the determination

TABLE XI

CAROTENE AND XANTHOPHYLL OF PLASMA IN DIABETES

	CAROTENE γ PER 100 ML.			XANTHOPHYLL γ PER 100 ML.		
	INSULIN PER DAY			INSULIN PER DAY		
	OVER 10 UNITS		UNDER 10 UNITS	OVER 10 UNITS		UNDER 10 UNITS
	INFECTIONS		INFECTIONS	INFECTIONS		INFECTIONS
	NONE	PRESENT	NONE*	NONE	PRESENT	NONE*
N	29	7	28	29	7	28
M	128	104	112	103	74	87

*There were no infections at time of observation in persons receiving less than 10 units of insulin.

were tabulated separately. It will be observed that in each group both the carotene and the xanthophyll content of the plasma were higher than normal, and that the more severe group had the higher carotinoids. The elevation of carotinoids may be due in part to the high carotinoid content of the diet. But since the diet of the more severe diabetic cases did not contain more carotinoids than that of the milder group, it seems likely that in patients with diabetes the carotinoids are not so readily changed to colorless compounds as in normal persons. In 15 diabetic cases under good control the mean vitamin A content of the plasma was 19.7 units per 100 ml. In 2 diabetic cases not under good control, the vitamin A content of the plasma was below 10 units per 100 ml. More studies are needed before a low vitamin A content of plasma can be regarded as characteristic of diabetes.

Celiac Disease (Table XII).—As a rule, the serum and plasma in cases of celiac disease are practically colorless because of their low content of lipochromes. Analysis showed in only 2 of 12 of our cases a normal content of carotene or total carotinoid, and in only 3, normal vitamin A. The ingestion of halibut liver oil failed to cause a normal rise in the vitamin A of the plasma, probably as a result of poor absorption.[7, 10] The present observations indicate that when the plasma carotinoids are low in a person consuming a normal diet who, without fever or hepatic disease, is suffering from malnutrition, and in whom diarrhea may or may not be present, then the diagnosis of celiac disease must be considered. In such cases increased fat in the stool, "flat" blood sugar curves after standard doses of glucose, and "flat" vitamin A tolerance curves after ingestion of halibut liver oil will establish the diagnosis.

Jaundice (Table XIII).—During the acute stage of infectious hepatitis (catarrhal jaundice) the carotene, xanthophyll and vitamin A content of the plasma were found to be low. As the jaundice subsided and as the stools became colored with bile, the plasma returned to normal. The important cause for the abnormally low values is probably faulty absorption. During the acute period of the disease studied, the absorp-

TABLE XII

CELIAC DISEASE

HOSPITAL NO.	C	X	A	TOTAL C	REMARKS
50364			14.0		
50364			19.0	61	After 1 year
47229			8.0	7	
47229			14.0		After 2 years
47229			23.5	24	After 3 years
J. M.			9.0	0	
44698			13.0	30	
105685			12.0		
108537			6.0		
108537			30.0		After 1 month; improved
98940			12.0	0	
98940	54	24	13.2		After 10 months; not improved
69795			7.0		
102853			13.0	0	
99945	79	48	8.6		
122123	11	15	4.4		
Priv. pt.	42	32	3.5		
143163	58	75	8.3		

TABLE XIII

JAUNDICE

HOSPITAL NO. OR INITIALS	C	X	A	TOTAL C	REMARKS
					Acute infectious jaundice
39158				45	Third day
Priv. pt.				53	Fourth day
43007				25	Fifth day
41141				54	Eighth day
71671	79	62	15.0		Fourteenth day
65755	30	32			Second day
5050	50	57	5.0		Fourteenth day
5050			10.0		Twenty-fifth day
27681			1.6		During attack
27681	84	59	21.5		Eight days after
					Other types
17732			6.0	76	Icterus gravis
13436			0	29	Congenital obstruction, bile ducts

tion of vitamin A is almost entirely prevented. In the 2 cases studied during convalescence, we found that the ingestion of oils rich in vitamin A caused an abnormally high concentration in the plasma (5 to 8 times that expected in normal persons). It seems probable, therefore, that infectious hepatitis so affects the liver that the rate of storage for vitamin A is decreased for several weeks. In one case of congenital obstruction of the bile ducts, no vitamin A was found in the plasma. In one case of icterus gravis, the vitamin A content was low, but the carotinoids were abnormally high for the age. The stool contained xanthophyll in large amounts.

Disorders of the Thyroid.—Animals deprived of the thyroid gland are unable to convert carotene to vitamin A.[8] Such animals, after having received thyroxine, are again able to convert carotene to vitamin A. Large doses of thyroid substance or of thyroxine cause lowering of the vitamin A content of the liver. We might therefore expect to find low values of plasma vitamin A both in hypothyroidism and in hyperthyroidism, and high values of plasma carotene in hypothyroidism, and low values in hyperthyroidism. In the 2 cases of hyperthyroidism which we have observed, the carotinoids and vitamin A of the plasma were low.

Hypothyroidism (Table XIV).—In the majority of our cases high values for plasma carotene were found; in all cases low values for vita-

TABLE XIV

CAROTENE, XANTHOPHYLL AND VITAMIN A CONTENT OF PLASMA IN HYPOTHYROIDISM

HOSPITAL NO. OR INITIALS	C	X	A	REMARKS
62833	233	90		Myxedema
101922	344	66		Xanthosis
R. C.	238	100	10.4	Dry skin; lethargic
R. C.	203	64	18.1	Received thyroid 1 month
18441	88	66	2.1	Cholesterol 418
88501	87	40	12.6	Hypothyroidism; hypoglycemic convulsions; basal metabolic rate, -22%
107827	203	113	8.4	Plasma cholesterol 310; convulsions
105237	213	87		Hypothyroidism ?
126439	234	78	9.9	Hypothyroidism ? Plasma cholesterol 273
Priv. pt.	170	75	12.6	Basal metabolic rate, -37%
141713	126	58	7.0	Hypothyroidism ? Plasma cholesterol 216; basal metabolic rate, -27%
120514	121	44	13.7	Hypothyroidism ? Plasma cholesterol 184; basal metabolic rate, -32%
Priv. pt.	97	65	16.2	Hypothyroidism ? Plasma cholesterol 195; basal metabolic rate, -35%

min A were found. The peculiar yellowish discoloration of the skin in hypothyroidism may be due in part to xanthosis cutis. In several cases we have observed that when sufficient thyroid substance was administered to cause elevation of the basal metabolic rate and lowering of the blood cholesterol, the carotene and vitamin A content of the blood tended to become normal.

Nephrosis and Nephritis (Table XV).—The carotene, xanthophyll and vitamin A of the plasma may be considerably elevated in chronic

TABLE XV

CAROTENE, XANTHOPHYLL AND VITAMIN A CONTENT OF PLASMA IN NEPHROSIS AND NEPHRITIS

HOSPITAL NO. OR INITIALS	C	X	A	TOTAL C	REMARKS
62416			88		Chronic nephritis with edema
62416			71	226	Chronic nephritis with edema, 2 mo. later
110305	284	204			Chronic nephritis with edema
E. F.	117	60	99		Chronic nephritis with edema; terminal stage
E. B.	227	108	44		Chronic nephritis; no edema
E. B.	328	136	40		Chronic nephritis; no edema
98332	232	128			Nephrosis; inactive
74030			24	141	Nephrosis; recovered
88125			60	104	Nephrosis; active
88125	149	72			Nephrosis; recovered after 5 months
56752			23	206	Nephrosis; duration 4 months
56752			46	393	Nephrosis; duration 5 months
56752			151	283	Nephrosis; duration 5½ mo.; more edema and albuminuria
56752			184	300	Nephrosis; duration 5½ mo.; more edema and albuminuria
56752			87	268	Nephrosis; duration 6 mo.; improved
56752			55	285	Nephrosis; duration 7 mo.; greatly improved
56752			44	215	Nephrosis; duration 7½ mo., apparently cured (no recurrence in 6 years)
89870	238	185	15.6		Nephrosis; remission
89870	185	90	124		Nephrosis; relapse

glomerular nephritis—with or without edema—and in lipoid nephrosis. In our cases xanthosis cutis did not occur. We have no explanation for this observation. The concentration of vitamin A in the plasma may attain elevations which we have observed in no other disease—elevations which normally can be produced only temporarily by administering large doses of the vitamin. Two observations at autopsy, in cases of chronic glomerular nephritis, revealed high values of vitamin A in the plasma, in spite of very low values in the liver. This observation sug-

gests that renal damage either may interfere with the capacity of the liver to store vitamin A or may cause liberation of the vitamin from the liver.

SUMMARY

The observations recorded in this paper clearly indicate the effect of the intake of carotene and xanthophyll upon the carotinoid content of the plasma. Relatively large amounts of those substances may pass through the placenta to the fetus. Vitamin A probably also passes through the placenta, but the fetus may also be able to form vitamin A from carotene. Normal infants and older persons readily absorb carotene from the diet or from solutions of carotene in oil, but the rate of absorption is slower than the rate of absorption of vitamin A. The low carotinoid content of the diet in early infancy and in the winter months explains the lower concentration of carotene and xanthophyll in the first six months of life and in the winter months. The mean vitamin A concentration of the plasma in normal persons reaches a constant level soon after birth and is not affected by season. The variations between single determinations are great. Infection causes a prompt and considerable fall in the concentration of carotene, xanthophyll and vitamin A in the plasma. This fall is due, in part, to low intake during infection, but is also due, in part, to fever. A few days after the temperature becomes normal, the vitamin A content of the plasma may rise considerably above normal.

Xanthosis cutis in normal persons, in diabetics, and in hypothyroidism is associated with an increase of carotene in the plasma, less often of xanthophyll. In severe untreated diabetes the tissues may not be able to metabolize carotene rapidly. In nephrosis and in severe chronic nephritis hypercarotinemia may occur without xanthosis cutis. In Bright's disease the level of plasma vitamin A may be greatly elevated, probably because the liver fails to store it. In hypothyroidism the carotinoids of the plasma may be elevated and the vitamin A may be low. Successful treatment with thyroid substance corrects the anomaly. In celiac disease the carotinoids and vitamin A are not readily absorbed.

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EXPERIMENTAL THERAPY OF ACUTE LEUCEMIA WITH EXTRACTS OF BONE MARROW

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THE nature of leucemia and leucemic diseases has been the subject of much speculation, and the conceptions of its character have been based only on certain similarities between the symptoms or the pathologic lesions in the disease and those of other conditions the nature of which is somewhat better known. The two hypotheses which are most frequently mentioned have attributed the disease to a neoplastic change or to infection. Neither of these is supported by proof, and the analogies are not especially convincing.

The *neoplastic hypothesis* is founded on the presence of extensive active proliferation of cells in the marrow and blood, the secondary local tumorlike masses often containing mitoses in distant organs, and, in some cases, certain clinical symptoms such as anemia, asthenia, and loss in weight, which are common to malignant tumors. In addition, the proliferating cells in leucemia are usually radiosensitive as are certain neoplastic growths. On the other hand, leucemia differs considerably from malignant tumors in that the latter originate in a single group of cells which proliferate locally, while the stimulus to proliferation in leucemia is widespread and affects not a single group of marrow cells but most if not all of the marrow tissue of the body. The secondary organ and tissue metastases in leucemia, also, while composed of proliferating cells, do not tend to invade the surrounding tissue in the manner of malignant neoplasms. In those instances in which the leucemic cells spread from the edges into adjacent tissue, the morphologic appearance is not that of a malignant tumor but rather that seen in the slow infiltration of wandering inflammatory cells. The chief resemblance to a neoplastic type of disease is in those cases of leucemia with hyperleucocytosis while those without leucocytosis and with only slight or moderate infiltrations have little in common with newgrowths.

The *infective hypothesis* is suggested chiefly by those cases of acute leucemia in which such symptoms as toxemia and prostration, purpura, and fever often high and of a septic type have simulated the picture of an acute infection. This view has been apparently supported by the presence in certain instances of preceding or accompanying lesions of an infectious origin in the mouth or throat, although such recognizable infections are relatively inconstant. Chronic forms of leucemia show no

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striking clinical resemblance to infections. Against the infective hypothesis it has been urged that no bacteria have been isolated from the blood or tissues except in occasional instances in which obvious severe intercurrent or terminal secondary infection was present; that no organisms are visible in microscopic examination of leucemic tissues nor do the tissue lesions suggest infection; that although an invisible filtrable virus cannot be excluded as the causative agent, the symptoms and course of leucemia do not resemble those characteristic of virus disease; that there is no evidence of the transmissibility in human beings; and that in age and sex selectivity leucemia differs from those diseases resulting from infections.

The present paper concerns certain experimental observations made at the St. Louis Children's Hospital on patients with acute leucemia to test the validity of a new and different hypothesis as to the nature of the disease. This hypothesis assumes that acute leucemia is due to an acquired defect in normal marrow function characterized by the inactivation or destruction of one of the normal factors in hematopoiesis. Before stating the hypothesis in more detail, certain observations about acute leucemia will be reviewed.

The primary site of the disturbance in leucemia is the bone marrow. In the chronic myelogenous type this has never been questioned, since the cells involved are obviously myelogenic. In the acute forms of childhood, the hyperplastic abnormal nongranular leucocytes characteristic of the disease were earlier thought to be abnormal lymphocytes, and the disease was spoken of as "acute lymphatic leucemia." However, even in the acute forms the marrow is the principal seat of generalized and extensive cellular hyperplasia. In addition the abnormal cells in the circulating blood have been shown[1] to contain abundant proteolytic ferment and in this respect resemble closely myelogenous cells (granular leucocytes) and differ from lymphocytes which do not possess such proteolytic activity. This is additional evidence that the cells in acute leucemia are of myelogenous origin, probably myeloblasts, and that the bone marrow is the organ chiefly involved. The most constant characteristics of the blood in acute leucemia are associated with an aplasia of the normal formed elements, all of which have their origin in the bone marrow. Thrombopenia and anemia are constant as well as a marked decrease in the granular leucocytes. Of the few granular cells present, many are young and immature so that a disturbance in maturation of the granular leucocytes is one of the striking features of the disease.

In the mechanism of normal marrow hematopoiesis there must be certain chemical factors which regulate the development and maturation of the leucocytes. The delicate balance and lability of this mechanism are constantly demonstrated. It is possible that the production of these specific substances (maturation factors) controlling such development and maturation of marrow cells may be injured or inhibited by certain

types of toxic injury. As examples of disturbances in such regulating mechanisms may be mentioned that involving the control of erythropoiesis by the liver fraction effective in the relief of pernicious anemia, the control of sugar metabolism by insulin, and the maintenance of calcium balance by parathormone. In poisoning by benzol, radium and roentgen irradiation, the resulting granulopenia is conceivably due to an injury of the enzymes or other factors which control the maturation of granular cells. The defective granulopoiesis constant in acute leucemia may therefore have its origin in the toxin-produced deficiency of a substance necessary to normal leucocytic development.

In attempting to explain the origin of such hypothetical toxic injury in acute leucemia, it is of interest that the disease has had a notable incidence among x-ray workers, and that acute bacterial infections have preceded the onset in a number of instances.

Regarding the proliferation of immature marrow elements and their appearance in the circulating blood in acute leucemia, it is possible that such a change is secondary to the disturbance in the mechanism of maturation mentioned, associated with failure of these young cells to mature, or to the eventual exhaustion of normal inhibiting factors. If one can assume that the physiology of normal blood formation depends on the continued presence of such specific actively secreted substances regulating cellular development and maturation, it is not difficult to conceive a later unrestrained proliferation of immature marrow cells such as are found in acute leucemia, when the normal control of the mechanism is lost and certain inhibiting factors are also lost or exhausted.

If one can attribute acute leucemia to toxic injury of a certain hypothetical factor concerned with maturation of the granular leucocytes, it follows that chronic myelogenous leucemia, in which there is an obvious overactivity in development and maturation of the granulocytes, might result from their excessive stimulation by a pathologic hyperfunction of the maturation process.

The conception of acute leucemia as a deficiency disease in which dysfunction of the marrow results from the absence of a secretion necessary for normal granulopoiesis suggested the possibility of testing such an hypothesis by attempting to supply the missing element through the parenteral injection of animal tissue extracts. After making a few observations with the use of extracts of liver, spleen, and thymus, without apparent effect, it was decided to study the effect of the injection of extracts of fresh red bone marrow on acute leucemia, and the results of these studies form the basis of this paper.

BONE MARROW EXTRACT IN ACUTE LEUCEMIA—EARLIER EXPERIMENTS

Preparation of Marrow Extract.—The earlier observations were made with several simple aqueous extracts prepared for me by Dr. G. H. A.

Clowes, of Eli Lilly and Company. These consisted of an aqueous extraction of finely ground beef ribs with a considerable volume of water, and later with 50 per cent alcohol. The extracts were combined, strained, evaporated to dryness *in vacuo* and defatted with gasoline. The residue was then taken up with water in proportion of about one part to ten and, after mixing twenty-four hours, was filtered through a Berkefeld candle. They were of a brown color and contained approximately 100 mg. of nitrogen per 100 c.c.

Injection into rabbits and guinea pigs showed no toxic effect and produced no constant change in the blood picture over several weeks. The action of two of the extracts on blood pressure was tested on dogs and one of them showed a definite pressor effect with increase in blood pressure of 12 to 15 mm. of mercury. The second extract had the usual depressor action of most tissue extracts. In children, subcutaneous or intramuscular injections were irritating and painful, the site often remaining tender and slightly swollen for a day or two, and at times a moderate febrile reaction lasting several hours followed the injections.

The effect of the marrow extracts on patients with acute leucemia in the St. Louis Children's Hospital was observed during a period of three years and brief summaries of several cases follow. In all summaries much irrelevant material and many details have been omitted although careful records were made over the many months of observation summarized.

CASE 1.—B. N., a 3-year-old boy, had been ill for three months when admitted on Sept. 9, 1931. He had had recurring fever, a poor appetite, and an increasing pallor. Within the previous month "bruised spots" had appeared on his legs from time to time, asthenia, some dyspnea, and enlargement of the cervical lymph nodes had developed, and four days before admission there had been a nasal hemorrhage lasting one hour. On examination, in addition to the skin hemorrhages, marked pallor and enlarged cervical nodes, the spleen and liver were both firm and easily felt below the costal margin, and the child was feverish and acutely ill. The blood showed 800,000 erythrocytes, 50,000 platelets, and 3,000 leucocytes of which 92 per cent were young nongranular mononuclear leucemic cells. The clotting time was 6 minutes and the bleeding time more than 10 minutes. One transfusion of 175 c.c. was given the day after admission following which the erythrocytes were slightly over one million.

On the fourth day after admission, marrow extract was given subcutaneously in doses of 2 c.c. and then increased to 5 c.c. daily. Little change was noted until the end of a week when the temperature, which had ranged from 38° to 40° C. (100.4° to 104° F.) and usually above 39° C. (102.2° F.), fell to normal (September 18), the enlargement of the cervical nodes disappeared, and the boy became alert, interested, and much improved clinically.

As clinical improvement continued, the spleen could no longer be felt (September 29), and he was able to be up in a wheel chair. During this time the red cells had gradually risen to 2,400,000 without further transfusion and the platelets were 150,000. The leucocytes, which had fallen to 1,500 a week after admission, had gradually risen to 6,200, and the granular cells were 45 per cent although abnormal leucemic cells were still present. Improvement continued

during the next two weeks, and the child was able to walk around the ward. The temperature remained below 38° C. (100.4° F.), appetite was good, and the patient had gained 4½ pounds. There were no complaints except pain from the subcutaneous injections of marrow extract. The red count rose to 3,500,000, the platelets remained above 100,000, and the leucocytes varied from 9,500 to 12,700 with 34 to 41 per cent granular cells. Marrow extract injections which had been given daily for thirty days were discontinued on October 12.

A week later the patient had become cross and irritable, the spleen had increased in size to the level of the umbilicus, leucocytes had risen to 21,500 with only 3 per cent granular cells, and the erythrocytes had fallen to 2,300,000. Bone marrow extract injections were resumed in doses of 5 c.c. twice daily (Oct. 19), but the condition changed little except for the appearance of a number of skin hemorrhages, an epistaxis which required transfusion, and an increase in leucocytes to 35,000. By the end of two weeks (November 1), however, there was considerable clinical improvement, and the spleen had again receded in size and the leucocyte count had fallen to 3,000 with only 1 to 3 per cent granular cells. Clinical improvement continued, and by November 16 with increasing appetite the patient regained 3 pounds he had lost during his relapse, although blood during this time had remained leucopenic and granulopenic.

At this time the leucocytes began to rise and during the next month ranged from 6,000 to 12,000 with the granular cells varying from 16 to 24 per cent. The general clinical condition remained good, although the spleen became slightly larger. Shortly after the onset of this improvement in the blood, the marrow extract previously used became exhausted and a different preparation was employed. This second extract produced several somewhat severe and alarming reactions of an allergic type (edema of the face, hives, cyanosis and dyspnea) on several occasions and it was given only every second day in smaller doses. During the following month the leucocytes varied from 4,000 to 12,000 with the granular cells from 16 to 24 per cent, and the platelets from 50,000 to 80,000. There were no hemorrhages, and the patient was alert, active, and cheerful although the extract injections produced slight fever and occasionally allergic symptoms.

By December 14, the clinical condition was unchanged. There were no more allergic reactions, but, after each injection, the patient was feverish and listless and had just recovered from its effect by the time the next injection was given two days later. The extract produced very painful local reactions which persisted several days. The spleen had become considerably larger, but the blood continued essentially the same and erythrocytes had remained somewhat over 2,000,000 with no transfusions for more than two months. On December 28 he became much worse, with vomiting, fever which rose rapidly to over 40° C. (104° F.), and the granulocytes fell to 3 per cent of 7,000 leucocytes. Epistaxis and hematuria developed, high temperature continued, and death occurred Jan. 1, 1932. Necropsy showed leucemic infiltrations but no manifest evidence of infection.

Comment.—Distinct abatement of the leucemic toxic symptoms followed the continued use of bone marrow extract, and the blood also showed considerable improvement. There appeared to be a recession of the disease without true remission. The fact that the child recovered from a rather acute toxic phase of leucemia and lived four months with relatively mild symptoms from the disease was unusual and unexpected, and was attributed to the bone marrow therapy. The recurrence of acute leucemic symptoms shortly after injections were discontinued and

their later recession, together with improvement in the blood after the extract was resumed, was also encouraging.

CASE 2.—B. B., a 5-year-old girl, had had scarlet fever 2 months before admission to the hospital on May 24, 1932. The cervical nodes had remained swollen, the child had lost weight and became progressively more pale; high fever together with large and small skin hemorrhages had been present for the week preceding. On examination, the patient was pale and acutely ill with fever of 40° C. (104° F.), cervical glands much enlarged, with axillary and inguinal glands and spleen slightly enlarged, many skin petechiae and ecchymoses. The blood showed anemia (2,700,000), thrombopenia, and 5,500 leucocytes of which 95 per cent were nongranular large leucemic mononuclear cells.

Bone marrow extract was started immediately in doses of 2 c.c. twice daily, and two transfusions were given. The temperature remained high for three days but thereafter fell to around 38° C. (100.4° F.), and the patient became clinically better. In the next two weeks this improvement continued, and the child was afebrile after a cervical abscess was incised and was able to be up in a wheel chair. The granulocytes rose to from 16 to 18 per cent without other change in the blood.

The child remained in the hospital six months with relatively slight change in her clinical state. She received marrow extract almost daily and several transfusions. During much of the time she was up in a wheel chair, cheerful, with good appetite and gaining slightly in weight. Once an abscess developed at the site of an injection and had to be drained. At times she was irritable and had some fever for periods of several days. There were no further hemorrhages, and the spleen remained only slightly enlarged. The leucocyte count varied from 5,000 to 12,000 except for one period of ten days during which it rose temporarily to 20,000 to 30,000 a few weeks after admission. The granular cells remained from 8 to 12 per cent, and the platelets continued to be less than 100,000. On Nov. 6, 1932, she developed a lobar pneumonia and died five days later. No necropsy was obtained.

CASE 3.—G. M., 5-year-old boy, had been pale and weak for three months when admitted to the hospital on Oct. 14, 1932. He had enlarged cervical lymph nodes, a palpable spleen, anemia (1,460,000 erythrocytes), decreased platelet count, and 9,000 leucocytes, of which 97 per cent were large nongranular mononuclear leucemic cells. Treatment consisted of several transfusions and, later, marrow extract injections. During the following six months there was only slight clinical improvement, but the patient remained cheerful and comfortable, although chronically ill. The blood continued typically leucemic, and once the leucocytes reached 46,000 although most of the time the count was less than 15,000. The granular cells remained low, and thrombopenia continued. Biopsy section of a cervical lymph node was typical of acute leucemia. In the seventeenth week he developed an acute otitis and temporary hemolytic streptococcus septicemia with the appearance a few weeks later of metastatic infectious foci near several joints which required incision, but which did not heal well. Death occurred in the twenty-seventh week after admission (April 19, 1933). No necropsy.

CASE 4.—B. B., a 2½-year-old girl, whose increasing pallor for three months had been the only symptom, was seen first on April 13, 1934, with a slightly enlarged spleen and a few small skin hemorrhages, leucocytes 5,500 with 96 per cent nongranular leucemic cells, platelets greatly reduced, and erythrocytes 1,700,000. Bone marrow extract injections were given daily, and the erythrocytes were brought to 3,000,000 by transfusion. She improved clinically and during the next three months was comfortable and without complaints, gained 3 pounds in weight; the erythrocytes remained about 3 million without transfusion. Occasionally transient fever was

noted. Leucocytes showed little change, ranging from 3,000 to 6,000, although the granular cells at times increased slightly, at one time reaching 35 per cent but usually varying from 10 to 15 per cent

Marrow extract injections were discontinued after two months, and four weeks later fever appeared with subsequent skin petechiae and finally a severe intestinal hemorrhage followed by *B. coli* bacteremia, terminal bronchopneumonia, and death on July 14, 1934. No necropsy was obtained.

CASE 5.—C. M., 6-year-old boy, had had anemia for two months and slightly enlarged cervical lymph nodes for one month before admission on Feb. 25, 1934. He was asthenic and had a palpable spleen but no hemorrhages or fever. The blood was typical of acute leucemia without leucocytosis, and biopsy of an inguinal lymph node showed typical leucemic infiltration. During the following six months he received several transfusions and daily marrow extract injections for considerable periods, with no significant change in the blood picture at any time. Much of this time the patient was comfortable, happy, but moderately asthenic. At certain periods he was able to be up in a wheel chair. During the second month intercurrent hemolytic streptococcus infection of the ears and mastoid occurred and subsided, and in the third month a cervical abscess had to be incised. The spleen became moderately enlarged, but there were no hemorrhages.

Early in the sixth month the patient became rapidly much worse, the cervical nodes and spleen increased greatly in size, there developed obstructive orthopnea with inspiratory retraction of the interspaces, edema of the face, brassy cough, and slight cyanosis, and fluoroscopic examination showed an increased mediastinal shadow. Although he had been receiving injections of a marrow extract every second day during this time, the substitution of another extract in slightly larger daily doses was immediately followed by a somewhat dramatic clinical improvement. The orthopnea disappeared within a day or so, and there was very definite decrease in the size of the cervical and other nodes and the spleen. These changes seemed too prompt and striking to be merely coincidental. No alteration in the blood occurred although the enlargement of glands and spleen had receded. The patient remained listless and asthenic but without complaints. Appetite continued fairly good, and there were no hemorrhages. Three weeks later he died suddenly and somewhat unexpectedly (August 20) after an attack of vomiting and abdominal pain. There was no necropsy.

CASE 6.—C. M. L., a 6-month-old colored girl, with pallor of 2 months' duration was first seen June 12, 1934. All lymph nodes were visibly enlarged, spleen and liver greatly swollen, and the blood count showed 304,000 leucocytes all nongranular mononuclear leucemic cells. After three daily injections of marrow extract, the leucocytes were 5,000 with 13 per cent granular cells; the lymph nodes, liver, and spleen had decreased in size so strikingly that they were barely palpable. Fever, thrombopenia, and granulopenia persisted although the total leucocyte count remained low, and the infant died about four weeks after admission of bronchopneumonia and bullous impetigo. There was no necropsy.

Comment.—In Cases 2 to 6 the results of the marrow therapy were considerably less encouraging than in Case 1. In certain instances there was some increased maturation of granular cells, but the changes in the blood picture were relatively transient and not especially striking. Clinically, one patient (Case 2) recovered from a rather alarming acute, febrile, toxic state apparently caused by the leucemia in a short time after the injections were started, and in two other patients (Cases 5 and

6) there was rather prompt and striking shrinking of lymph nodes and spleen. Clinical improvement in the general condition was common, and four of the children lived somewhat longer periods (three for six months, and one for three months) in the hospital than is usual for patients with acute leucemia. They had relatively few acute symptoms and were comfortable and happy, although somewhat asthenic, for long periods. In one instance (Case 4) more acute symptoms recurred after the marrow extract was stopped, and two children (Cases 3 and 5) were able to resist severe acute streptococcus infections for a number of weeks. In these cases it seemed possible that the marrow extracts had been of some benefit in arresting the progress of the disease.

During this period several other children were admitted to the St. Louis Children's Hospital with acute leucemia but died in a few days or were removed when the diagnosis was made. The only patient under observation more than a week received marrow extract injections for 12 days with no apparent effect.

The results described were considered of sufficient interest to warrant further observation on the effect of marrow extracts but difficulty was encountered in devising a method by which red marrow could be secured sufficiently fresh and in adequate amount for preparing extracts. Eventually through the interest and cooperation of Mr. Charles Heim, Superintendent of the American Packing Company of St. Louis, such material became available. Mr. Heim devised and had made a machine for this work which would rapidly and cleanly break up fresh beef ribs into small bits; it was possible to start the preparation of an extract within 2 hours after the animal was killed.

BONE MARROW EXTRACTS IN ACUTE LEUCEMIA—LATER SERIES

Preparation of Later Extracts.—Ten pounds of fresh macerated beef ribs were extracted with 7,500 c.c. of water to which sufficient concentrated hydrochloric acid had been added to make 3 per cent by volume. After two hours the mixture was strained, and the residue again extracted for two hours with a like volume (7,500 c.c.) of 1.5 per cent hydrochloric acid. After straining off the coarse material, the residue was brought to pH 7.0 with sodium hydroxide. This appeared to be the isoelectric point for the protein present, and it was readily removed by filtration, leaving a water-clear filtrate. This filtrate was then concentrated rapidly in an evaporator, by which warmed air was fanned continuously over flat pans and drawn off by suction, the temperature of the extract being kept below 40° C. When the volume had been reduced to somewhat less than 10 per cent of the original, the extract was filtered and was sterilized by passing through a Mandler candle. Each 100 c.c. of the concentrated extract represented approximately one pound of the original ground ribs.

These extracts were clear, neutral, and of varying degrees of amber tint. They had a high content of sodium chloride and considerable calcium and phosphate. An analysis of five separate preparations showed a total nitrogen content varying from 128 to 265, nonprotein nitrogen from 93 to 151, and the coagulable protein nitrogen from 9 to 154 mg. per cent. They were not toxic when injected subcutaneously into laboratory animals in doses of 2 to 5 c.c.

Since subcutaneous injections in children were extremely painful and irritating, a very limited use of the extracts during the next year or so resulted because it did not appear justified to subject children regularly to so much pain and discomfort. During this time the irritating salts were dialyzed out of one extract, but a single patient treated with this preparation showed no apparent effect, and no further effort at purification was made. To avoid the local irritation, it was later decided to inject the extract intravenously, and in 1936 it was used in 10 c.c. doses diluted to 50 c.c. with sterile water in a patient with acute leucemia without any discomfort from the injection. He showed very slight clinical improvement following the injections but died from a severe pulmonary hemolytic streptococcus infection a few days later. In subsequent use of the extracts the intravenous route was employed routinely, usually in amounts of from 2 to 5 c.c. diluted several times with water and given slowly. The largest amount given has been 20 c.c.

Several case reports showing the results with these concentrated extracts follow:

CASE 7.—R. G., a 16-year-old boy, who had lost 25 pounds in a month and had several severe nosebleeds, was first seen Dec. 28, 1936, after having received several transfusions. There was no complaint except some weakness, and examination revealed a huge spleen which extended below the navel, enlarged inguinal lymph nodes and a slight erosion on the left nasal septum which had a tendency to bleed and require packing. There was no anemia but a definite thrombopenia, and the leucocytes numbered 105,000 with more than 90 per cent nongranular mononuclear leucemic cells. Daily injections of marrow extract were started and continued in doses of 2 to 3 c.c. intravenously.

During the following month the patient was quite comfortable, with fairly good appetite; he had no complaints but gradually lost weight. Severe epistaxis continued at intervals and necessitated several transfusions. There was no change in the size of the spleen. The erythrocytes remained around 2,000,000; the leucocytes fell gradually to 39,000, but the granulocytes increased to 25 per cent, although 8 per cent were immature forms; and the platelets remained low.

At one time during this period a transfusion of chronic myelogenous leucemia blood was given this patient. The donor was an adult in the same blood group (O) who had a total leucocyte count of 450,000 with typical clinical and blood picture of chronic myelogenous leucemia. No clinical change or detectable alteration in the blood picture of the recipient followed this transfusion.

In the second month there was little clinical change, and the patient remained cheerful, was without fever and spent much time sitting in bed reading. Because of severe nasal hemorrhage, transfusions had to be given several times to keep the

red count above 2 million. The leucocytes continued to fall and reached 4,000 (February 28), but with 53 per cent granulocytes, while the platelets remained much decreased.

The third month in the hospital was complicated by several febrile infections, tonsillitis in the first week, from which he apparently recovered. The appetite became poor, weakness increased, hemorrhagic oozing continued from the nose, and after irregular fever for two weeks the patient died March 28 with hemolytic streptococcus sepsis. During the last month of life the leucocytes varied from 4,000 to 20,000 but the granular cells remained high (40 to 65 per cent) although pathologic leucemic cells were always present and thrombopenia persisted. Necropsy showed in addition to typical leucemic infiltrations of the viscera, bronchopneumonia with pulmonary abscess, serofibrinous pleurisy, and general peritonitis (hemolytic streptococcus).

Comment.—Although there was little clinical improvement in this patient and thrombopenia persisted, with recurring hemorrhage from an ulceration on the nasal septum, the hyperleucocytosis disappeared and there was a rather striking increase in granular cells in the blood, many of which were mature. Also, the disease did not progress as rapidly as was anticipated on admission, and three months elapsed before terminal intercurrent infection occurred. The transfusion of chronic myelogenous leucemic blood was tried only because of the possibility that the overactivity in maturation and development of the granular cells in chronic myelogenous leucemia might be associated with the presence in the blood of factors which could be transferred to a patient with acute leucemia. The experiment was apparently harmless and the result inconclusive.

Case 8.—W. H., a 5½-year-old boy, first seen July 24, 1937, had a history of gradually increasing pallor and weakness for six weeks. There was a slight general glandular enlargement and the submandibular nodes were considerably swollen, firm and tender. Many petechiae and a few ecchymoses spotted the arms and legs. The liver extended two fingerbreadths below the costal margin, and the firm spleen reached below the umbilicus. The blood picture was typical of acute leucemia, with prolonged bleeding time (9 min.) and clotting time (4 min.); very few platelets; 2.5 million erythrocytes with 45 per cent hemoglobin; and 7,000 leucocytes of which 97 per cent were abnormal nongranular mononuclear cells of the leucemic type. On admission to the hospital he was acutely ill and moderately toxic, with fever of 39° C. (102.2° F.) On the face and scalp were a number of impetigo lesions of two days' duration, and the left knee was somewhat swollen and tender. During the following week hemolytic streptococci were grown from the blood on two occasions and additional localizations developed in the right shoulder and right leg. The picture then was that of streptococcus sepsis with severe toxicity and continued high fever (39° to 40° C.). An area of pneumonia had developed in the left lung by the end of the second week, and new skin lesions continued to appear; the arm and leg foci remained swollen and painful; and the fever and toxicity persisted unabated. There was little change in his condition during the third week except that the temperature was slightly lower and the pneumonic area cleared. The prognosis was considered hopeless and death imminent.

Two days after admission intravenous injections of marrow extract were started and continued daily in doses of 2 to 4 c.c. for four days. After the fourth injection the cervical nodes had regressed until they were no longer visible although they were still palpable. The spleen, which had been below the umbilicus, was barely

palpable and three days later could not be felt. The extract injections were later continued every second or third day. The blood showed little change from the first examination except that a leucopenia varying from 600 to 3,000 developed, the thrombopenia continued, and the granulocytes were only 1 to 3 per cent. By the end of the first week when streptococcus sepsis was apparent, two transfusions were given, and sulfanilamide was started and continued in doses of 1.0 gm. (15 gr.) three times daily. Marrow extract injections were continued from two to three times weekly.

In the fourth week a series of remarkable changes occurred. The infectious focus in the right upper arm which had subsided somewhat, suddenly became more swollen and fluctuant, and those in the right and left legs simultaneously suppurated. The temperature fell to 38° C. (100.4° F.) within a few days, and the boy was definitely improved and more alert. On examination of the blood, it was found that the leucocytes had increased from 4,600 on August 18 to 14,000 on August 24 with abundant platelets (798,000), 73 per cent granulocytes, and no abnormal cells. The abscesses were incised and drained without excessive bleeding. Smears showed

Fig. 1.—Five-year-old boy (Case 8) during remission of acute leucemia.

pus cells and many gram-positive cocci in chains and some in clumps, but on culture only *Staphylococcus aureus* was grown.

With the incision of the abscesses, improvement was continuous, the wounds healed, and the patient was happy and playful. The temperature remained below 38° C. (100.4° F.) After four weeks a mild pneumonitis with fever of 38° to 40° C. (100.4° to 104° F.) lasting a few days caused some concern, but the pulmonary signs and shadow disappeared within a week or so. For a period of two months the only other symptoms were moderate asthenia and slight fever. The boy gained several pounds, was cheerful and happy, and was able to walk around the ward (Fig. 1). The color remained good, and no transfusion was necessary for a period of six weeks. The blood examination continued to show abundant platelets; the total count varied from 8,000 to 19,000, the higher figure being obtained during the acute pulmonary infection. Granular cells varied from 40 to 80 per cent.

In the seventh week after the first sudden change in the blood picture the leucocytes began to increase in number and within a few days (Oct. 12) reached 50,000, with the granulocytes being reduced to about 10 per cent. A great reduction in platelets and the return of young nongranular mononuclear leucemic cells were noted. Following a increase in marrow extract injections, the leucocytes fell within a week

to 9,000, but there was no change in the differential picture and the platelets remained low. During this time there was little change in the patient's clinical condition and he remained alert, playful and happy in spite of a fever of about 38.3° C. (101° F.) The spleen which had not been palpable for more than two months began to enlarge again and within ten days reached the umbilicus (Oct. 23). There was very slight enlargement of the axillary and cervical nodes, but a few ecchymoses were noted (October 25) on the legs. During the following week he became more irritable and feverish. The terminal picture was a *Staphylococcus aureus* septicemia with multiple skin and subcutaneous abscesses, and death occurred Nov. 13, 1937. No necropsy was allowed.

Comment.—The rather remarkable clinical and blood remission in this patient developed suddenly and the reappearance of granular leucocytes in the blood was accompanied by prompt suppuration of metastatic infectious foci which had previously been indolent. The recovery from a generalized streptococcus infection which appeared hopeless was also entirely unexpected and was attributed to sulfanilamide therapy. The recurrence of an acute leucemic blood picture almost two months later was soon followed by a return of clinical signs of the disease, and neither was affected by continued marrow therapy.

CASE 9.—I. M., a 3-year-old girl, was first seen Sept. 6, 1937, with high fever of several days' duration and anemia for two months. Physical examination was negative except for a fever of 40.7° C. (105.3° F.), and a mild tonsillitis of Vincent's type. There was no glandular or splenic enlargement. The blood revealed an anemia of 2,250,000 erythrocytes (40 per cent hemoglobin), thrombopenia (37,000), and 42,000 leucocytes, of which 98 per cent were nongranular mononuclear leucemic cells. Treatment with daily intravenous injections of marrow extract and transfusions was started immediately. The temperature remained above 40° C. (104° F.) for five days but fell to normal within the next four days; she remained afebrile thereafter, except for an occasional slight rise attributed to the intravenous injection. Within three days after admission the leucocytes had fallen to 3,200 without other change in the blood except an increase in erythrocytes to 3 million as a result of transfusions. Clinical improvement continued and two and one-half weeks after admission (September 22), the leucocytes were 8,200 with a normal-looking differential count in which there were 20 per cent relatively mature granular neutrophiles, and a very definite increase in platelets. At this time she was able to be up and was running about the ward (Fig. 2). The spleen was not enlarged but at times could be palpated at the costal margin. During the next four weeks, the patient continued active, afebrile, and without complaints except occasionally transient abdominal pain. The erythrocytes remained at 4.5 to 5 million without transfusion, and the leucocytes ranged from 6,800 to 13,000 with 22 to 30 per cent granular cells, most of which were segmented. Of the lymphocytes, only careful scrutiny prompted by a knowledge of the diagnosis of leucemia revealed that some still had characteristics suggestive of young nongranular leucemic cells. The platelets numbered 170,000, and many were of an abnormally large size. Marrow extract injection had been given about three times weekly. The weight increased 3 pounds while she was in the hospital.

Since the patient lived at a distance and had improved so much, it was decided to discharge her for a visit to her home; this was done on Oct. 15, 1937. A blood count made by her physician the following week showed 21,200 leucocytes with 92 per cent lymphocytes, and she was brought back to the hospital. During this week

she had had no marrow therapy, but it was resumed on readmission (October 22) and continued in doses of 2 to 5 c.c. three or four times weekly for the next six weeks. During this time the child appeared well and was able to be up and about, had good appetite, no fever or other complaints, and gained 2½ pounds. The spleen remained just palpable, and one brief epistaxis occurred during this time. The blood, however, was definitely leucemic and apparently unaffected by the marrow injections. Leucocytes varied from 12,000 to 69,000 and were typical nongranular young leucemic cells, the granular cells being less than 5 per cent. The platelets continued to be of large size, and the count also remained very low (25,000).

The erythrocytes decreased gradually to 2 million, and two transfusions brought their number back to over 4 million but produced no change in the leucocytic picture. The leucocytes numbered 34,000 with 2 per cent granular cells at the time of discharge, on December 7, when the patient was again taken home and received no

Fig. 2.—Three-year-old girl (Case 9) during remission of acute leucemia.

further treatment. She remained asymptomatic for a week and then became quite irritable, complained of abdominal and joint pains, and developed increasing asthenia and pallor. Three weeks after discharge (December 22) she had a profuse and continued epistaxis with fatal exsanguination.

Comment.—This patient recovered promptly from a toxic febrile attack, hyperleucocytosis disappeared, and the blood remission and clinical improvement which followed shortly were striking and persisted for several weeks. That the recurrence of a leucemic blood picture was related to the discontinuing of the marrow extract injections is doubtful although with their resumption the weight increased and there were no clinical signs of disease for a number of weeks.

CASE 10.—S. D., a previously healthy 18-month-old girl, was first seen Nov. 14, 1937, with multiple skin ecchymoses and fever of a week's duration. Very slight general glandular enlargement, a considerably swollen liver and spleen, and fever of 38.8° C. (101.7° F.) were the only physical signs. Leucocytes numbered 43,000 with 97 per cent nongranular mononuclear leucemic cells, platelets much reduced (58,000), and a slight anemia (4,000,000) with 8.5 gm. hemoglobin.

In the following two months, during which the patient was given two series of injections of marrow extract intravenously and several transfusions, there was continued anorexia with loss of weight, and a progressive anemia. A month after admission the leucocytosis had disappeared, and the total count was 1,500 to 3,000 with granulopenia and thrombopenia. Fever persisted and an acute bilateral otitis media developed followed by chronic ear discharge. At one time severe hematuria lasted several days.

In the tenth week (Jan. 19, 1938) after admission, the temperature fell to normal, and the blood, which on the previous day had shown thrombopenia, 5,200 leucocytes with 10 per cent granulocytes, was found to have 4,900 leucocytes with 68

Fig. 3.—Extensive bilateral parotid swelling in 20-month-old girl (Case 10) during blood remission. (From 16 mm. film.)

per cent granulocytes and no abnormal cells. The platelets had become abundant (328,000). From this time the clinical improvement was rapid, and the patient was discharged two weeks later (Feb. 5, 1938) with a normal leucocyte count (7,900) and differential (6 stab, 48 segmented cells, 44 lymphocytes, and 2 monocytes), abundant platelets and no anemia.

The following eleven weeks the patient spent at home and was seen weekly at the hospital for observation, blood examination, and an injection of marrow extract. During the first month she gained 5½ pounds and was active, playful, and apparently in normal health although a slight chronic otorrhea persisted and both the liver and spleen remained considerably enlarged and firm. The erythrocytes rapidly rose to over 5,000,000 and leucocytes varied from 7 to 12,000 with a normal differential picture, the granulocytes ranging from 24 to 52 per cent. In the sixth week at home (March 16) a bilateral soft swelling of the parotid glands was first noted. These gradually increased in size and five weeks later they had become quite firm, as large as lemons, with much edema of the face and eyes, and with a similar swelling also of the submental tissues. The clinical appearance was that of Mikulicz's syndrome. She was readmitted to the St. Louis Children's Hospital (April 25), and for

a period of two weeks large doses (5 to 20 c.c.) of the bone marrow extract were given intravenously each day with no apparent effect on the swellings which continued to enlarge until she could not open her eyes (Fig. 3). There was no fever, and the leucocytes still ranged from 6,800 to 8,000 with 44 to 60 per cent granulocytes and no detectable abnormalities in the smear.

Biopsy of a cervical lymph node in the region of the parotid was performed on May 5, and the pathologic report by Dr. H. B. McCordock follows:

"The original architecture of the lymph node is obliterated by a dense tumorlike growth of one type of cell which replaces the germinal centers and obscures the sinuses. Dense masses of new formed cells infiltrate the connective tissue framework of the node, but not the capsule. The infiltrating cells are slightly larger than small lymphocytes and contain coarsely reticular and deeply stained nuclei. The cytoplasm is so scant that it can be recognized with certainty only in isolated cells which infiltrate connective tissue spaces. Mitotic figures are numerous."

Although the danger of irradiation in acute leucemic states was appreciated, the continued growth of the parotid masses, the fact that the blood picture had been normal for more than three months, the microscopic appearance of the excised lymph node, together with parental insistence that something be done, combined to induce the trial of x-ray therapy over the tumor masses. During a period of ten days (May 9 to May 18) nine irradiations totaling 1,250 roentgen units were given. Ten days after the last irradiation the swellings had almost completely disappeared. No change occurred in the blood until the day of the last irradiation (May 18) when the leucocyte count dropped from 4,900 to 1,500, the granulocytes from 40 to 15 per cent, and the platelets became noticeably scarce. By the end of the following week (May 26) the leucocyte count was to 6,200 with only 3 per cent granulocytes, and another biopsy on a cervical lymph node showed (Dr. H. B. McCordock):

"Large masses of abnormal white cells replace the germinal centers and medulla. The trabeculae are thickened but not infiltrated. The peripheral lymph sinuses remain apparent and contain numerous leucocytes. The abnormal cells resemble immature lymphocytes or blast forms. The nucleus shows a fine chromatin structure, and there is a distinct nuclear membrane. A few eosinophilic myelocytes are found intermingled with the other cells. The changes resemble those seen in lymph nodes from cases of acute leucemia."

On June 1, leucocytes were 29,400 and on June 6, 34,200 all except one per cent being nongranular mononuclear leucemic cells. Death occurred on June 9, just one month after the first irradiation. During the last ten days of life, there developed fever, asthenia, irritability, and hemorrhages from the mouth and nose. No necropsy was permitted.

Comment.—Of special interest in this patient were the abrupt change in the blood picture with sudden loss of leucemic characteristics in a fashion similar to that observed in a patient cited previously (Case 8): the complete blood remission which lasted four months, the appearance of parotid and glandular swellings during the remission, which suggested a neoplastic growth, the rapid recession of these swellings after roentgen irradiation, and the recurrence of the clinical and blood picture of acute leucemia obviously produced by the irradiation.

The parotid tumors clinically were considered to be related to the leucemia-lymphosarcoma ("leucosarcoma") type but the biopsy section of an adjacent lymph node strongly suggested a metastatic neoplasm and appeared distinct from the usual picture of lymphosarcoma or leucemia.

Another node removed three weeks later, after irradiation, when the swellings had receded and the blood picture of leucemia had returned, showed only the characteristic appearance of an acute leucemic gland.

CASE 11.—L. M. G., a 13-year-old girl, was first seen Dec. 19, 1937, because of pallor and asthenia which had been increasing for three months. There had been pains in the extremities and within the week previous to admission, fever of 102° F. had been noted together with hemorrhagic areas in the skin of the legs and ankles and some bleeding from the gums. Examination showed, in addition to the hemorrhages, that the liver and spleen were greatly enlarged but there was no lymphatic glandular adenopathy. Bleeding time was 11 minutes; erythrocytes numbered 1,800,000; platelets, less than 50,000; leucocytes, 57,300 with only 1 per cent granulocytes and the remainder mononuclear leucemic cells.

She was immediately started on transfusions and daily intravenous injections of marrow extract. During the following two weeks uterine (menstrual) bleeding was so profuse that she had to be given 3,500 c.c. of blood. By this time the leucocytes had fallen to 3,500, and the granulocytes were 19 per cent without other change in the blood picture. Clinically she improved very little during the next month and required a total of 13,500 c.c. of blood in 40 transfusions because of continued profuse bleeding, chiefly from the nose, before her death on Feb. 2, 1938. The liver and spleen remained large. The marrow extract injections were continued daily except for two periods of several days each. The leucocytes varied from 2,000 to 14,000 but the granulocytes rose steadily so that during the last month they formed from 28 to 68 per cent of the total. Abnormal leucemic cells persisted, however; the platelets remained very low; and hemorrhages continued. Fever was present during most of the illness and about three weeks before death a severe streptococcus infection of the arm at the site of a venipuncture developed which showed little tendency to heal. Clinical signs of peritonitis were noted terminally, but permission for necropsy was not obtained.

Comment.—In this patient, as in Case 7, there was a marked decrease in the abnormal circulating leucemic cells, and the granular leucocytes showed an unusual rise. Both patients suffered from continued severe hemorrhages which persisted in spite of transfusions.

In addition to the patients whose cases have been summarized, several other children with typical acute leucemia were given marrow extract injections for periods of a week or less without apparent effect on the blood. In two children the injections were continued for from six weeks to two months. Neither showed any definite clinical improvement or change in the granulocytes. In one there was no significant alteration in the blood picture, while in the other, although well-marked reduction occurred in the number of leucocytes after a few weeks, this could not be fairly attributed to the bone marrow therapy. Both eventually died from intercurrent infection.

Besides the experimental observations on children with acute leucemia, five patients with typical chronic myelogenous leucemia were also given the marrow extracts. Three of these were children, and two were adults. In only one was any marked change in leucocytes observed. This patient, a child of 5 years, apparently early in the disease, showed on

several occasions an increase in leucocytosis after the injections, followed by a decided drop in the count. A complete study of this patient with relation to the extract could not be made since irradiation therapy was later used, and he was not available for further observation. In view of the previously stated hypothesis, which assumes an increase in the leucocytic maturation factor for chronic myelogenous leucemia—the reverse of the condition in acute leucemia—no improvement in this type would be anticipated from the extract injections.

DISCUSSION

A review of the patients with acute leucemia treated with bone marrow extracts shows two (Cases 8 and 10) with complete remission of the disease of two and four months; two (Cases 1 and 9) with similar complete remissions for shorter periods; two (Cases 7 and 11) with marked increase in maturation of granular leucocytes; four (Cases 2, 3, 4, 5), in whom the disease remained clinically arrested or quiescent for from three to six months; two (Cases 5 and 6), in whom rather prompt decrease in size of leucemic enlargements of the lymph nodes and spleen was noted after the therapy was given; and other patients in whom neither the clinical course nor the leucemic blood picture was affected.

That the bone marrow extract therapy employed was responsible for any or all the favorable changes observed is without proof. All patients received transfusions at intervals, and other symptomatic treatment. It is true, however, that of 50 patients with acute leucemia reported[2] from the same clinic and under observation during the ten years preceding these experiments, who were also given frequent transfusions, none showed anything suggesting a remission or any increase in granular leucocytes to the degree observed in certain patients here reported. In these earlier patients, once the typical acute leucemic blood picture became evident, the blood remained leucemic, and the disease progressed, usually rapidly and without clinical arrest or remission, to a fatal termination.

The possibility that the favorable results in the patients reported might be related to fortuitous chance must be considered, and it is conceivable that certain of the instances of apparent general clinical improvement without blood change may have been merely coincidental. It is possible also that the instances in which toxic febrile states were alleviated and those in which leucemic swellings receded rapidly after the extract injections were chance observations. The increase in maturation of granulocytes, however, is more difficult to account for as accidental, and to include also the patients who had remissions in the leucemic blood picture would appear to stretch the already long arm of coincidence to an unusual degree. Remissions in acute leucemia have not been observed previously by the writer, and must be rare, since a single instance[3] was found in the literature. The general attitude of

physicians regarding the improbability of remission in the disease is illustrated by the following experience: Two of the patients reported (Cases 8 and 9) were under observation in the hospital at the same time and were shown at a clinic attended by a number of physicians as examples of acute leucemia with complete clinical and blood remissions that had lasted a number of weeks. At this time both children appeared well (Figs. 1 and 2) and were able to walk into the room. The only comments elicited after their presentation indicated great skepticism as to the verity of the diagnosis of acute leucemia.

The abruptness with which the appearance of the blood may change is illustrated by the observations on two patients (Cases 8 and 10) who had complete restoration to a normal blood picture. In one (Case 8) the change was so unexpected that differential blood examinations had not been made for a week previous to the recognition of the blood remission, but in this period the granulocytes rose from 3 to 73 per cent, the platelets from less than 50,000 to 798,000 and the leucemic cells disappeared. In the second patient (Case 10) the blood had been leucemic on the day previous, and restoration to a normal blood picture occurred within twenty-four hours. Such abrupt changes in the circulating elements have been noted previously in the opposite direction with the development of leucemia in patients under observation in "preleucemic" states. In a previous report[4] such a patient was cited whose blood changed from 21,500 leucocytes with 72 per cent granulocytes to 140,000 with 11 per cent granulocytes a week later, while Borchardt[5] records a patient whose leucocytes rose within two days from 14,000 with 93 per cent polymorphonuclears to a leucemic picture of 91,800 leucocytes with 94 per cent "lymphocytes."

The evidence furnished by the experimental observations with bone marrow extract in acute leucemia in support of the hypothesis of dysfunction of the marrow related to maturation of the granular cells is, of course, inconclusive. It is of interest that in at least six instances (Cases 1, 7, 8, 9, 10, 11) there was an unmistakable and striking increase in granular leucocytes in the circulating blood during the treatment with the extracts.

It must be remembered that the extracts were prepared empirically and that, if they contained any specific substance, no test for potency was available. The only test was to determine whether patients with acute leucemia responded favorably to their administration; there was, therefore, always the possibility that certain patients showing no improvement may have received extracts with little activity or that age or other influences had altered their potency. A few observations of their effect on the blood of laboratory animals showed no constant changes in the leucocytes but this was not considered conclusive, since, for example, the liver fraction valuable in pernicious anemia produces no change in the erythrocytes of normal individuals.

If any specific potency is present in the marrow extracts used and if the changes observed were related to the replacement of some deficiency in a physiologic mechanism, it is obvious that the stimulation was inadequate and incomplete since even those patients with remissions relapsed and a later continuation of the injections was relatively impotent. Indeed the impression gained through many of the observations was that a definite effect on the disease was produced but that it was only partial and imperfect, as though only one of possibly several necessary substances was being supplied and that only sufficient to modify to a greater or less degree the progress of the disease.

Acute leucemia is universally considered a constantly fatal disease beyond the reach of therapy. It is hoped that the experiments here reported will appear sufficiently encouraging to warrant further investigation in the development of a potent biologic product which may be of value not only in treatment of the disease but in establishing its character.

SUMMARY

The hypothesis is suggested that acute leucemia may be related to a deficiency in physiologic factors which are necessary for the maturation of the granular leucocytes in the marrow.

A series of experiments is reported in which children with acute leucemia were treated by injection of extracts of bone marrow in an attempt to replace the missing maturation factors in hematopoiesis. Of the patients treated, four had more or less complete remissions of the leucemic state, and in several others there was evidence of considerably increased maturation of the granular leucocytes.

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THE IMPORTANCE OF DEFICIT OF SODIUM AND CHLORIDE IN DEHYDRATION

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THE following two cases are reported to show that the central feature of the syndrome called dehydration is loss or deficiency of sodium and chloride. In the case of the burn, the mechanism of the loss of sodium chloride would not lead to loss of water; in the case of diarrhea the course during recovery indicated that there was a deficiency of salt but not of water. These cases will be used as a background for the discussion of certain newer concepts of dehydration, particularly as to the therapeutic implications.

CASE REPORTS

CASE 1.—The patient, a boy slightly more than 3 years old, who had a severe burn with deficit of sodium and chloride, and acidosis, was admitted to the surgical service. An hour earlier he had overturned a pan of boiling water and scalded most of the skin of his right leg, about half of his left leg, and a large area on the lower part of his back. He was immediately placed in a continuous, warm tub of water to which salt was added. He was in the tub for about 60 of the first 64 hours. His temperature rose to 40° C. within 24 hours. About 12 hours after admission he

TABLE I

CONCENTRATION OF SERUM IN CASE 1

DAY	H CO_3 MEQ./l	CL. MEQ./l	PROT. %	N.P.N. MG. %
2.5	11	80	5.3	
3.5	22	96	4.9	16
12	20	69		
13	23	97	5.8	
17	22	100	6.8	23

had a convulsion lasting 15 minutes. A hypodermoclysis of 800 c.c. of physiologic saline solution was given at this time followed by a transfusion of 125 c.c. of blood 8 hours later. Again the next day (about 36 hours after admission) he had another convulsion and was again given a hypodermoclysis of salt solution. In the afternoon he was semicomatose and about 64 hours after admission in extremis. At this time the pediatric service was consulted. He was breathing rapidly and deeply, his eyes were sunken, his pulse rapid and feeble. A sample of blood showed marked decrease in concentration of chloride and bicarbonate (Table I). He was immediately given an infusion of hypertonic sodium chloride and bicarbonate (the sodium chloride and sodium bicarbonate contained in 1,000 c.c. of interstitial fluid added to 500 c.c. of normal saline) and 250 c.c. of compatible serum over a period of 5 hours. The drip was continued for a total of 42 hours with salt and glucose solutions. When the continuous infusion was started, the tubs were discontinued and the denuded areas

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sprayed with gentian violet (2 per cent). The temperature became lower and the boy looked much better within 12 hours. Chemical recovery was good the next morning (12 hours after starting the continuous drip). The treatment with gentian violet was continued for 6 days when the crusts were loosened by saline soaks and 15 minutes in a saline tub on the first day. The next day the tub was used for 4 hours and the following day for 9 of 12 hours during the day but not at night. During this day he lost his appetite and fever became higher (40° C.). The following day he was treated for only 4 hours in the tub when it again became obvious that he had developed severe salt deficit. The symptoms of circulatory collapse and dehydration were the same as before, but signs of acidosis were absent. (Breathing was Cheyne-Stokes.) The tubs were again discontinued and continuous infusion of hypertonic solution of sodium chloride and bicarbonate started. Recovery was again rapid. Thereafter his course was essentially satisfactory although he remained in the hospital for a total of ten weeks. The skin showed islets of epithelial tissues when the tubs were discontinued the second time. These were later supplemented by skin grafts.

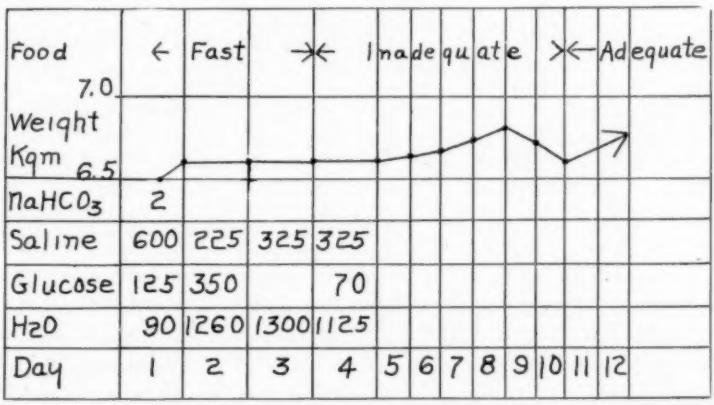

Chart 1.—The curve represents the course of the weight. The food intake is represented as "fast" when no food was given by mouth; by "inadequate" when the calories were less than 70 per kilogram, and "adequate" when over 70 calories per kilogram. One dose of 2 gm. of sodium bicarbonate was given by mouth. Saline is represented in cubic centimeters of 0.9 per cent sodium chloride by hypodermoclysis. Glucose is represented in cubic centimeters of a 10 per cent solution by intravenous infusion. Water is represented in cubic centimeters taken by mouth. Signs and symptoms of dehydration and acidosis were absent on the second day but diarrheal stools were still passed. On the third day the stools were practically normal.

During the first 10 days the white blood count was 25,000 to 30,000 per cubic millimeter. The urine was negative except that the specific gravity was always below 1.010 and on three occasions 1.005 during the first three days.

Summary.—A 3-year-old boy with an extensive burn developed symptoms of acidosis and salt deficit after spending about 60 of 64 hours in a tub containing salt. Improvement was rapid with continuous infusion of hypertonic sodium chloride and sodium bicarbonate. Symptoms of salt depletion again returned when the tub was again used for about 13 of 48 hours.

CASE 2.—The patient, 7½-month-old boy, had diarrhea with otitis media, acidosis, and deficit of sodium chloride. He had been artificially fed since birth and ap-

parently was doing well until the present illness. Nine days before admission he developed a cold. Six days before admission he had many watery stools which did not contain blood. Two days before admission he started to vomit and probably vomited all his food and most of the water offered him during the two days before he was admitted to the hospital. On admission he was extremely sick, with greatly diminished skin turgor, sunken fontanels and eyes, Kussmaul breathing, and sunken abdomen. Both middle ears contained pus. The baby was treated with 2 gm. of sodium bicarbonate by mouth and was given subcutaneous injections of physiologic saline and blood transfusions. No food was given for three days, during which time urine and stools were collected for chemical analysis. Recovery was satisfactory. The course of the case is represented in Chart 1 and the metabolic results are given in Table II. Before treatment was started the serum showed the following concentrations: bicarbonate 14 mM. per liter; chloride, 108 mM. per liter; total base, 137 mM. per liter; total protein 6.8 per cent; and nonprotein nitrogen 65 mg. per cent.

TABLE II

OUTPUT IN CASE 2

	DAY	VOLUME C.C.	CL. MM.	P. MM.	FIXED BASE MEQ.	CA. MEQ.	N. GM.
Urine	1	380	12.0	10.1	7.1		3.4
Urine	2	214	4.2	2.4	0.1		0.6
Urine	3	214	4.8	1.1	1.6		1.0
Stool	1	350	28.1	3.0	47.9	3.1	1.8
Stool	2	250	13.2	2.8	18.7	2.3	0.6
Stool	3	76	1.8	0.4	2.3	0.0	0.1

The points to be noticed are: (1) marked decrease in concentration of serum total base on admission; (2) recovery from all symptoms and signs of dehydration within 24 hours; (3) excretion of negligible amounts of the administered sodium chloride and bicarbonate in the urine and stools; (4) retention of larger amounts of sodium and chloride not accompanied by a gain in weight. This last point is particularly important since no gain in weight indicates no increase in total body water. In other words retention of sodium chloride and sodium bicarbonate were responsible for re-establishing a normal distribution of body water.*

DISCUSSION

Underhill[1] first emphasized the significance in burns of the high concentration of hemoglobin and low concentration of blood chlorides. He later proved that the localization of chloride in the edematous reaction at the site of the burn was sufficient to explain the changes in the blood.

*The above argument neglects the water freed from the cells because no food was given except the intravenous glucose. While an exact calculation of the water freed from cells cannot be made, it is too small to affect the argument. Analyses were not made to demonstrate that recovery of normal concentration of serum sodium had taken place when clinical recovery was apparent. Furthermore the metabolic studies do not differentiate between sodium and potassium, and all conclusions assume that the excretions were largely sodium. We know that this was probably not the case but the assumption merely minimizes the amount of sodium retained. I have no real apologies for the plan of the metabolic work on this case since it was completed ten years ago shortly after I left Dr. Marriott's clinic. The work was never published because at the time I was unable to explain what recent experimental work has made obvious.

This work has been repeatedly confirmed[2, 3, 4] and Blalock has emphasized the importance of loss of plasma proteins as well as salt, in the production of shock in patients with burns. It was not surprising, therefore, to see obvious signs of acidosis, dehydration, and shock 60 hours after the burn. However, the marked reduction in concentration of chloride was not anticipated, since the patient had received 1,700 c.c. of physiologic saline in the previous 50 hours. Since this amount of saline is equivalent to one-half the sodium of the extracellular fluid of a boy of this size it is not likely that this quantity of salt was immobilized at the site of the burn. Before the second episode, no salt solution had been given, the inflammatory reaction about the burn was subsiding, and there was no vomiting, diarrhea, nor other of the usual means of salt loss. The mechanism of the loss of sodium chloride in the two episodes was not obvious until it was discovered that the tubs were only receiving enough sodium chloride to make a solution of about one-third physiologic strength. Obviously the surface denuded of skin permitted free diffusion of extracellular electrolyte from the tissue spaces and capillaries into the hypotonic water of the tub. By this process the body would lose sodium and chloride, but not water. Nevertheless, the patient showed symptoms and signs of loss of extracellular fluid, since the blood was concentrated with respect to hemoglobin and skin turgor was diminished. The low concentration of chloride was due to loss of sodium and chloride, but the evidences of loss of extracellular fluid and decrease in blood volumes were not due to loss of water from the body but rather due to shift of extracellular water into the cells.*

The state of the boy was analogous to that produced by Yannet and myself[5] in dogs. In these experiments, when loss of extracellular electrolyte was induced without change in total body water, the dogs developed all the symptoms and signs of clinical dehydration; the blood was concentrated with respect to red cells and serum proteins but the concentrations of serum sodium and chloride were reduced. Skin turgor was diminished. Analysis of red cells showed that water had gone into the red cells. It was shown that the changes in the volume of extracellular fluid indicated that water must have gone into other cells as well. This shift of water from extracellular spaces into the cells fits into prevailing concepts of the type of equilibrium that must exist between fluid on the two sides of cellular membranes. In other words basic and probably also acid ions do not cross cellular membranes in living cells in response to changes in osmotic pressure. Hence when loss of extracellular electrolyte (sodium and chloride) makes extracellular fluid hypotonic, osmotic equilibrium is attained by a shift of extracellular water into the cells.

*In view of the low concentration of serum chloride on the third day, it is likely it was equally low at the time of the two convulsions. If this be true, the convulsions were analogous to those seen in experimental water intoxication. The improvement after administration of physiologic saline solution fits in with this interpretation.

As has already been pointed out, the baby with "intestinal intoxication" was also not suffering from loss of total body water but rather from dehydration of extracellular fluids and increased hydration of intracellular fluids owing to loss of sodium and chloride. The observations upon which this concept rests are the low total base in serum on admission and the clinical recovery with retention of sodium and chloride but not of water.

It now seems clear that in most clinical types of so-called dehydration, the loss of sodium and chloride is greater than that of water. This is indicated by the fact that reduction in the concentration of sodium is more frequently encountered than normal or high concentrations. This is true in diabetic coma,[6, 7] diarrheal diseases,[8] nephritis,[9] miner's cramps,[10] Addison's disease,[11] etc. It follows, therefore, that physiologic saline or its equivalent is the most important therapeutic measure in dehydration. Experimental and clinical observations indicate that losses of sodium and chloride in cases showing marked dehydration may be equal to the amount contained in one-third of the extracellular fluid of the body, i.e., the amount contained in 70 c.c. of physiologic saline (or equivalent) per kilogram of body weight. In treatment this amount of salt may be necessary to restore body sodium and chloride and thereby re-establish normal distribution of body water.

Actually no rule can be given as to how much sodium chloride must be given to a dehydrated patient. Recovery from clinical evidences of dehydration and a diuresis containing chloride may be used as guides. However, in adrenal-cortical insufficiency and in certain cases of hyposthenuric nephritis, excretion of chloride occurs even when body chloride is deficient. For these reasons, in addition to the amount of saline necessary to produce a diuresis, estimations of the probable deficit of salt and of the probable amount which continues to be lost should be used in deciding on the dose of saline.

The above discussion brings out the reason why the administration of sodium and chloride as physiologic saline is the most important therapeutic procedure used for restoration of the normal distribution of body water in dehydration. The following paragraphs will point out briefly the treatment of renal insufficiency, disturbances in acid-base equilibrium, and shock, which frequently accompany deficiency of extracellular electrolyte.

Since the kidneys normally regulate the concentration of serum electrolyte as well as excrete nitrogenous waste products, the disturbances in acid-base equilibrium as well as elevation in nonprotein nitrogen may be regarded as brought about by renal insufficiency. If the abnormalities be considered as due to a deficit of body water, intravenous glucose and water by mouth should be the mode of treatment. Clinical experience and experimental studies[12, 13] show that the abnormalities of renal func-

tion continue to a greater or lesser degree as long as the deficiency of sodium and chloride persists, while administration of sodium chloride quickly restores renal function.

During deficiency of extracellular electrolyte, studies on dogs[12] and humans[13] indicate that the glomerular filtrate is reduced in volume, and urea is reabsorbed to a greater extent than normal by the renal tubules. This accounts for the high nonprotein nitrogen and perhaps also for the fact that water is excreted more slowly than normally. If small deficits of sodium exist, the kidneys may eventually restore electrolyte concentrations in serum by excreting water.[12, 14] However, if large deficits are allowed to persist the concentrations of serum electrolyte remain low because the kidneys do not diminish the volume of extracellular fluid in order to preserve concentrations. Nevertheless, large amounts of water may be excreted when the deficit of extracellular electrolyte remains marked, provided the intake is large. The disturbances in acid-base equilibrium are explained by the fact that, when large deficiencies of extracellular electrolyte are present, the kidneys fail to excrete the relative excess of chloride in acidosis and the relative excess of sodium in alkalosis. It is not clear what is the explanation of all these anomalies; in part they are dependent on the circulatory failure but in part they are also probably dependent on the fact that the function of renal tubules is best carried out when serum concentrations are approximately normal.

Experimental and clinical experience shows that sodium chloride quickly re-establishes normal renal function when this procedure brings about the correct volumes and concentration of extracellular electrolyte. Administration of large amounts of water for urine formation is of secondary importance and is probably taken care of by the water in physiologic saline. When kidney function is not disturbed by actual renal disease, physiologic saline alone will usually correct the disturbances in acid-base equilibrium, because the kidneys can excrete the relative excess of chloride in acidosis, and saline replaces the relative deficit of chloride in alkalosis. However, in cases with marked acidosis, or when losses of sodium and chloride are likely to continue, or when oliguria or disturbed renal function exists, the administration of physiologic saline without sodium bicarbonate may aggravate or produce acidosis.[15] This effect is brought about chiefly by diluting the bicarbonate already in the body at a time when the kidneys are not excreting the relative excess of chloride of physiologic saline. In acidosis this effect may be serious, even when renal function is fairly good, if loss of sodium in excess of chloride continues to occur as in diarrhea. Under these circumstances a solution resembling interstitial fluid more closely than physiologic saline has theoretic and practical advantages. Hartmann and I have both come to this conclusion and developed slightly

different solutions resembling interstitial fluid.*† These solutions may be used in all types of dehydration.

The first patient illustrates the disadvantage of administration of physiologic saline while loss of extracellular electrolyte is taking place. Before the first episode, the boy received 1,700 c.c. of 0.9 per cent solution of sodium chloride. The salt solution undoubtedly postponed the development of alarming symptoms, but made it almost certain that deficit of sodium would be greater than deficit of chloride, and, hence, made acidosis a prominent feature. Before the second episode, no injections of salt solution were given and no acidosis developed. Confirming Hartmann,[15] we have observed analogous changes following administration of physiologic saline in diarrhea and renal insufficiency. For several years we have used a solution† resembling interstitial fluid in composition and have neither seen acidosis develop nor be aggravated during treatment. Administration of a balanced solution makes the use of special doses of bicarbonate (or its equivalent) seldom necessary.

Marriott[16] first pointed out the shocklike nature of dehydration, and Powers[17] brought out the importance of blood transfusions in therapy. This procedure is now recognized as the most important therapeutic measure for shock. Blalock[18, 19] and others have demonstrated that large amounts of extracellular electrolyte are immobilized at the site of traumatic injury and at the site of a burn. In this sense surgical shock is analogous to deficiency of extracellular electrolyte (dehydration) except that the sodium chloride is immobilized rather than lost from the body. Perhaps by shock one should refer particularly to the inability of the body to maintain blood circulation and blood pressure, not primarily because of cardiac failure, but rather on account of decreases in the volume of circulating fluids and loss of plasma proteins through capillary dysfunction. If plasma volume, blood pressure, and circulation remain insufficient for a few hours, secondary changes take place leading to dilatation of the capillaries and leakage of serum proteins into the tissue spaces. These features of shock may be prevented by blood (or plasma) transfusions and are sometimes corrected by the same means. However, if severe shock is allowed to persist several hours, no effective therapy is available. Since it is not possible to estimate which patients with dehydration will recover from shock with solutions of salt and glucose alone, it is necessary to give transfusions to many patients who would otherwise recover with only hypodermoclyses of saline and intravenous infusions of glucose.

Intravenous injections of glucose solutions produce such obvious improvements in many patients that their use is not always understood.

*Concentrated Lactate Ringers Solution, prepared by Eli Lilly and Company, Indianapolis, Ind.

†Concentrated Interstitial Salt Solution prepared by Sharp and Dohme, Philadelphia, Pa.

Glucose solutions supply the body with much needed food, and water without salt. Since excess of water over that in physiologic saline is not especially needed by a patient with low concentration of serum sodium, their use is chiefly as food and for treating shock by a temporary expedient while matching blood for transfusion, and perhaps as a general tonic through the effect of glucose on metabolism. Glucose solutions should not be given subcutaneously to patients with salt deficit since such injections immobilize the already depleted stores of sodium and chloride.[5] Glucose is specifically indicated in liver injury and perhaps in certain cardiac conditions.

SUMMARY

The case of a patient with severe burn is reported. Two episodes of symptoms of dehydration developed in which loss of sodium chloride without loss of water was produced by placing the boy in a continuous tub containing hypotonic salt solution. Symptoms of dehydration were due to loss of extracellular electrolyte without loss of body water.

Metabolic studies are reported on a patient with infantile diarrhea, which show that the symptoms of intestinal intoxication were brought about by loss of sodium and chloride without deficit of body water.

Therapeutic procedures for the treatment of dehydration are discussed in the light of recent concepts of the nature of dehydration.

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ACCOMPLISHMENTS IN MATERNAL AND CHILD HEALTH AND CRIPPLED CHILDREN SERVICES UNDER THE SOCIAL SECURITY ACT

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WITH the passage of the Social Security Act there again came into existence federal grants-in-aid to the states for maternal and child welfare. The program was broadened over that of the former Maternity and Infancy Act to include older children in the child health provisions, grants for medical and surgical care and hospitalization of crippled children, and grants for child welfare services for dependent and neglected children. The federal act makes it clear that the grants are intended to extend and improve conditions primarily for mothers and children living in rural areas or areas of economic distress. All states and territories are cooperating under the maternal and child health provisions, and all but one in services to crippled children.

MATERNAL AND CHILD HEALTH

Administration of Program.—Title V, Part 1, of the Social Security Act provides for the extension and improvement of maternal and child health services in the states through federal grants-in-aid administered for the Federal Government by the Children's Bureau of the Department of Labor and for the states by the state health agencies. Once the plan for services prepared by the state agency has been approved by the Chief of the Children's Bureau as in accordance with the Social Security Act, the program is directed and administered in its entirety by the state and local health agencies.

Of the $3,800,000 authorized for appropriation each year, $2,820,000 must be matched by the states; $980,000 is granted on the basis of the state's need for assistance in carrying out its plan and is not matched.[1]

In 1934 thirty-one state health agencies had bureaus or divisions of child health and of these only twenty-two were directed by full-time physicians.[2] Between 1929, when federal funds ceased to be available to the states under the Maternity and Infancy Act, and the passage of the Social Security Act in 1935, there had occurred a marked falling off in many states of both state and local appropriations for maternal and child health services and, because of the economic depression that was coincident, state health department budgets were cut, and general funds available previously for maternal and child health were reduced or entirely eliminated. On the other hand, it is encouraging to note that in a number

From the Children's Bureau, United States Department of Labor.

of states, maternal and child health activities established during operation of the Maternity and Infancy Act had been continued, indicating that the value of this work had been demonstrated to the people of these states.

In February, 1936, funds for maternal and child health services became available under the Social Security Act, and by June 30, 1936, 46 states, Alaska, Hawaii, and the District of Columbia had had plans approved and were receiving grants from the federal government. Plans for the two remaining states were approved before the end of the calendar year 1936.

Since, under the act, the responsibility for developing and submitting a plan is that of the state health agency, and since the needs of states vary widely because of special geographic, racial, agricultural, or industrial conditions, the plans that have been approved are very diverse in many respects. In certain respects, especially in regard to administrative features and types of basic services, the plans show similarities. The progress that has been made toward good administration, high standards of service, and a broader coverage for service may be briefly summarized.

All the forty-eight states, and Alaska, Hawaii, and the District of Columbia, have established divisions or bureaus of maternal and child health in the state health agency under the direction of a physician. In the spring of 1936, the Conference of State and Territorial Health Officers recommended to the Children's Bureau that the director of a division of maternal and child health in a state department of health should be a physician trained in pediatrics or obstetrics or both and preferably in public health as well. Today, of the 50 directors now in office, 30 have been trained in pediatrics, 5 in obstetrics, 6 have had previous experience in child health administrative positions, and 9 have had no specialized maternal or child health training or experience; all but 2 of these 9, however, have had general public health experience or training. Of the 50 directors, 22 have now had some training in a school of public health. Because of the many clinical features of a maternal or child health program, previous clinical training or experience has been considered by most state agencies to be a fundamental qualification for these positions. As the programs broaden and more and more local practicing physicians take part in rendering the service, this policy becomes increasingly important.

Additional physicians have been employed by forty-two states, either as administrative assistants or as clinical consultants. The plans for 1939 show that there will be twenty-eight pediatricians and thirteen obstetricians thus employed full time during the year.

Scope and Content of Program.—From the plans submitted by the several states, it becomes apparent that the functions of the state divisions of maternal and child health are as follows: (1) To seek the cooperation of the physicians of the state in extending statewide facilities for continuous health supervision throughout pregnancy, infancy, and

childhood, and in providing care for sick children and for women at delivery; (2) to seek the cooperation of physicians and all other citizens of the state in informing the public as to what is good maternity care, infant care, and care of children at different stages of growth and development, and how facilities for such care may be made available in each locality of the state; (3) to develop maternity and child health services in all parts of the state through local health units; (4) to aid in the organization of local health units through the provision of child health or maternity services in areas not yet fully organized; (5) to be responsible for the establishing of high standards of service in the maternal and child health field; (6) to cooperate with all other bureaus of the state health agency in activities affecting the health and welfare of children and mothers, such as public health nursing, control of communicable diseases, including tuberculosis and syphilis, collection and study of vital statistics, control of the milk and water supply; (7) to cooperate with other state agencies concerned with problems of child health or welfare, as the bureaus of child welfare, departments of education and the agriculture extension service of the departments of agriculture; (8) to cooperate with medical and other professional groups in providing facilities for postgraduate education in maternity care and care of children and the related fields of nutrition and dental care, and (9) to promote health education through the schools and the general public.

The maternal and child health services that are carried out under state plans are basically those commonly described as health supervision:

(1) Prenatal clinics and child health conferences conducted by physicians with the aid of public health nurses; (2) home visiting by public health nurses for teaching maternal, infant, and child hygiene, and for instruction in bedside nursing care, and (3) nurses' classes or conferences with mothers for educational or follow-up purposes.

In addition, planning for care of the mother at delivery and of the infant in the neonatal period is becoming widely recognized as one of the important services to be rendered by the local staff. In an increasing number of local areas provision is being made for home nursing care at delivery of women attended by physicians and of their newborn infants, as well as the more usual prenatal and postnatal nursing care. In a number of states the problems of the medical and nursing care of prematurely born infants are being given special attention.

The services of consultant obstetricians and pediatricians to assist general practitioners with their individual cases are being made available in special regions or localities of certain states where such services are not available to women unable to procure them from their own resources. In at least one state such services are supplied on a state-wide basis. Though the number of such projects is still limited and the territory and population covered are relatively small, a variety of methods of meeting the need for case consultation service are being explored with a view to

determining the most practical for use under different conditions. In eighteen states obstetricians or pediatricians are employed on a full-time salary basis for this purpose, usually to serve in a single district or county demonstration unit; in twenty-two states consultants are employed on a part-time salary or fee basis; and in four states specialists may be called for consultation from an approved list by general practitioners and payment is made on a case basis. Ultimately a study of the different methods in use should give information as to which conditions of employment and reimbursement permit a case consultant's services to be most fully and widely accepted, which conditions safeguard most surely the quality of the special consultation service, which plan of procedure defines most clearly the function of the case consultant as contrasted with the administrative consultant responsible for organization of the program, and most important of all, which plan results in raising most satisfactorily the general level of care rendered in the community.

During the current fiscal year, in 35 states, the District of Columbia, Hawaii, and Alaska, provisions are made for payments to practicing physicians for conducting prenatal and child health conferences and for school medical examinations. There is an increasing tendency on the part of the state agencies to enlist the aid of specialists in obstetrics and pediatrics in the state in setting up standards for the conduct of these conferences. A few states are establishing conference training centers for the general practitioners who will later take over the conduct of conferences in rural areas. If those conferences are to fulfill the purposes for which they are being established with regard to the individual served and to their influence on the character of medical practice in the community, they must measure up to the best practice in the community.

Last year under the provisions of the Social Security Act, prenatal clinics or conferences were conducted by physicians in 2,713 centers in thirty-six states. Child health conferences were conducted in 6,033 centers in forty-three states.

Interest in programs of postgraduate education for practicing physicians is increasing. In 1936 thirteen states conducted courses under the maternal and child health plan in cooperation with state medical societies; during the present fiscal year, 1939, thirty-nine states plan such courses. There is increasing evidence that the rural practitioners who care for such great numbers of mothers and children appreciate and are profiting by the courses which bring them not only factual information in obstetrics and pediatrics but stimulation to include health supervision and preventive procedures in their practices. The courses for local practitioners are creating a demand for short courses in obstetrics and pediatrics at medical centers where clinical observation and actual experience can supplement lectures.

Practically all state divisions of maternal and child health have conducted studies or surveys to better acquaint them with the health prob-

lems of mothers and children existing in their states. The majority of the studies have been concerned with infant and maternal mortality, a number of these in conjunction with the state medical societies; others have been special studies of the incidence of prematurity and stillbirths. Nutrition, immunization, and dental surveys have been conducted. These studies are all adding greatly to our knowledge of health conditions that actually exist in different parts of the country.

A steadily increasing number of states have added the services of one or more nutritionists to the staffs of the state health departments, usually in the divisions of maternal and child health, to serve as advisers to the medical, dental, and public health nursing staffs in matters related to nutrition of the family. On June 30, 1936, nine states had full-time nutritionists on their staffs. Today, twenty-four states employ forty-three full-time nutritionists, in most cases to serve in a statewide advisory capacity, in some to assist district or local staff in organizing local service or in rendering local service. The tendency is for the nutritionist engaged by the state to act as adviser to state and local staff and as a coordinator of service offered by different state or local agencies rather than to give individual case service. The value of a nutritionist in an urban health service has long since been proved, especially when there is coordination of service with the welfare agencies. In the rural areas the need is often greater than in the cities. Here the home economics specialist of the extension service may be working with many families, but her work may not be well coordinated with efforts of the health department staff. A nutritionist serving in a rural health unit can be of great assistance both in a general advisory and educational capacity and in giving case service when desirable. In a few rural areas service of this sort is being rendered.

The number of public health nurses probably constitutes a better index of actual services being rendered than any other one figure. To a great extent the effectiveness of the medical program depends upon the quality and the number of the public health nurses whose function it is to carry it into the home in understandable terms and techniques to the individual mother and child. This requires many skills and an understanding of human relationships which come only with proper training and experience under supervision. Most of the states have shown gratifying response to the recommendations of the state and territorial health authorities regarding the qualifications of the public health nurses employed by them. According to the 1939 maternal and child health budgets, the states have provided for the employment of 2,716 public health nurses or two-fifths of the total number of public health nurses working in the rural areas. In rural areas there is one public health nurse for every 11,000 persons in the population; in cities there is one for every 5,000 persons. The problem of adequate supervision and leadership for these public health nurses has been given serious consideration because of the

need for special guidance and assistance in maternity nursing and in many of the problems of infant care and care of young children. For the year ended June 30, 1938, specialized public health nursing consultants in maternal and child health have been appointed to the staffs of twenty-one state health agencies and in twelve additional states the chief nurse or at least one of the generalized supervisors has had special work in maternity care or care of children.

Cooperation With Professional and Lay Groups.—One of the conditions specified in the Social Security Act that must be met before approval can be given to the state plan by the Chief of the Children's Bureau is that the plan must provide for cooperation with medical, nursing, and welfare groups and organizations. Up to the present time this condition has been met largely by the formation of state maternal and child health advisory committees made up of representatives from state medical associations, other medical organizations, the state nurses' associations, the state welfare departments, special organizations for child welfare or public health, lay organizations such as parent-teacher associations, state federations of women's clubs, and organizations of farm women. In some states technical subcommittees have been appointed to work with the divisions of maternal and child health in developing the medical phases of the program. In forty states members of the Academy of Pediatrics are represented on advisory committees. In thirty-three states the state medical societies have appointed committees to act in an advisory capacity to the state boards of health in their maternal and child health programs. There is need for improvement in the functioning of the technical committees in order to make sure that the members of the profession in each state who have a real interest in the program and have much of value to contribute may do so.

In addition to the function of giving technical advice through professional representation, the advisory committees in many states are proving invaluable in promoting the understanding of, and gaining the cooperation of, large groups of citizens through representation of lay groups on the committees.

Unmet Needs.—During the two years and eight months that federal funds have been available to the states for maternal and child welfare, steady progress has been made by the states and local communities in making services available to mothers and children. Many rural areas previously without such service have been reached; many groups in special need have been served; the quality of work in most places has been improved; standards of care have been established and extension of service into new fields has taken place; a basis for administrative procedure has been established on the federal-state level and in turn between the states and local communities; a basis for acquiring facts with regard to the need and the extent of service is being developed. However, as progress has been made in establishing services, recognition of the gaps in the total

program and of specific needs has been inevitable. Facts regarding maternal mortality, mortality of infants on the first day and in the first month of life, and mortality and morbidity of older children are being widely studied. Ways to meet many of the needs are already well known, but resources are inadequate to provide the means to carry out the necessary steps in the program. That the amounts now available to the states are not adequate to fill their needs was made apparent by the state health agencies in submitting plans for maternal and child health services for the fiscal year 1939. In response to a question as to unfilled needs, twenty-eight states made statements of specific needs that in the aggregate amounted to $22,000,000 annually. These needs included funds for payment of physicians' fees for delivery and other medical care, hospitalization for maternity cases, additional public health nurses, additional prenatal and child health conferences, additional service of nutritionists, and additional public health units. Many other states made additional statements of need without specifying necessary personnel or costs.

The utter futility of providing means of assessing the health and welfare of children and of mothers and of not providing the means to maintain them in health or restore them to health if sick, or, in the case of maternity, to make available complete medical and nursing care of mother and infant has forced itself upon health and welfare workers and upon the people. The experience of two and a half years has made clear the great advances that could be made in maternity care, in the health supervision and medical care of children, and in the care of crippled children should facilities and resources for such care be made available to those unable to obtain good care.

Having come to the realization of the necessity for a courageous attack on the problem of maternity care and care of newborn infants that would meet the need with no half-way measures, national organizations and individual citizens have united in an effort to create public opinion favorable to action. The creation of the National Committee on Better Care for Mothers and Babies (now the National Council for Mothers and Babies)[3] early in 1938 was a timely development in view of the widespread public interest in the National Health Program presented by the Interdepartmental Committee to Coordinate Health and Welfare Activities at the National Health Conference[4, 5] in July, 1938. The need for an expanded program for maternity care and health supervision and medical care for children was included in the National Health Program as one of the major measures to be given precedence in the development of the proposed plan. Specific recommendations were made, following in general, as far as maternity care is concerned, the plan of action proposed at the Conference on Better Care for Mothers and Babies called by the Chief of the Children's Bureau in January, 1938.[3] Reference to the report of the Technical Committee on Medical Care to the National Health Conference shows that in the opinion of that committee a plan of gradual

expansion over a ten-year period is desirable in order that administrative procedures may be sound and standards of care and qualifications of personnel be maintained at a high level.

CRIPPLED CHILDREN'S SERVICES

Administration of Program.—Under part 2 of title V of the Social Security Act, relating to services for crippled children, an appropriation of $2,850,000 annually is authorized "for the purpose of enabling each state to extend and improve (especially in rural areas and in areas suffering from severe economic distress), as far as practicable under the conditions in such state, services for locating crippled children and for providing medical, surgical, corrective, and other services and care, and facilities for diagnosis, hospitalization, and aftercare for children who are crippled or who are suffering from conditions which lead to crippling." The total amount of the sums made available by the federal government must be matched by the state.[1]

Prior to the passage of the Social Security Act in 1935, public provisions for the care of crippled children were sporadic and uneven and in many states totally inadequate, if not altogether lacking. In only 28 states was there an official state agency authorized by law to provide care and medical treatment for crippled children. In many of these states appropriations were small and services were greatly limited.

By June 30, 1936, state plans had been approved for the administration of services for crippled children for 38 states. At the close of the fiscal year 1937, every state had designated an official agency to administer services for crippled children, and state plans had been approved for forty-two states and Alaska, Hawaii, and the District of Columbia. At the present time, forty-seven of the forty-eight states, and Alaska, Hawaii, and the District of Columbia are conducting services for crippled children under the provisions of the Social Security Act. Louisiana is the only state which has not submitted a state plan, and it appears likely that as soon as certain financial and administrative problems have been clarified, a plan will be submitted, thus making state services for crippled children available throughout the country.

The programs for crippled children are being administered by several types of state agencies. At the present time the department of health is charged with the administration of crippled children's services in 24 states; in 15 states, the department of public welfare; in 4 states, the department of education; in 5 states, a crippled children's commission; in 1 state, a university hospital, and in 1 state, an interdepartmental committee administers the program through the crippled children's division of the department of education. It is interesting to observe that there has been an increasing trend toward establishment of new programs in state departments of health and, in a few cases, transfer of administrative responsibility to state departments of health from other state

agencies. An appreciation of the inherent nature of the crippled children's program as one involving problems of medical care has undoubtedly influenced states in giving the administration of these services to the state health agencies. That the program for crippled children as set up under the Social Security Act is primarily one of medical care is also reflected in the types of personnel directing the state program of services. In 30 states a physician serves as director of the program; in 8 states, a nurse; in 3 states, a social worker; and in 9 states, a nonprofessional person.

Qualifications of Personnel.—Two years ago the Children's Bureau Advisory Committee on Services for Crippled Children appointed by the Secretary of Labor recommended that state agencies adopt standards for the selection of professional personnel which had been established by the various national boards for medical specialties such as the American Board of Orthopedic Surgery and the American Board of Pediatrics, or by recognized national professional organizations such as the National Organization of Public Health Nursing, the American Association of Medical Social Workers, and the American Physiotherapy Association. A review of state plans for the fiscal year 1938 showed that such standards were taken into consideration by state agencies in the selection of the various types of personnel as follows: surgeons, 24 states; nurses, 16 states; medical social workers, 19 states; and physical therapy technicians, 20 states. In many states, particularly those where difficulties have been encountered in obtaining local personnel who meet the qualification standards established by the national organizations, provisions have been made for further training of staff personnel.

A considerable number of public health nurses have received training in public health nursing, in orthopedic nursing, and in physical therapy. Several universities and schools of nursing have arranged their nursing curricula to serve to best advantage the trainee who is taking a supplementary course in public health nursing or in orthopedic nursing in order that she may return to the state equipped to serve as a consultant or to give direct service to crippled children. A number of social workers and physical therapy technicians have likewise been given additional training in their respective fields of work with crippled children. Educational centers have been interested in developing courses designed to equip workers in these special fields. The selection and training of personnel will require continuous attention if standards of service are to be maintained and steadily improved.

Standards for Hospitalization and Convalescent Care.—The recommendations which the Children's Bureau Advisory Committee on Services for Crippled Children made with respect to the selection of hospitals used for the care of crippled children have been of great assistance to the states in setting up standards for the selection of hospitals. With few exceptions the hospitals which are being used by the state agencies for

the treatment and care of crippled children are those that have been registered by the Council on Medical Education and Hospitals of the American Medical Association and that have been approved for surgical service by the American College of Surgeons. Additional standards have been established by state agencies in line with those recommended by the advisory committee with regard to facilities and personnel to meet the special needs of crippled children. As a result of the increased interest in the care of crippled children and the additional funds made available under the Social Security Act, many hospitals have improved their equipment to give more adequate care to crippled children.

Standards for convalescent homes and for foster homes have not as yet been well defined. However, in the selection of convalescent and foster homes the majority of state agencies are cooperating closely with the bureaus of child welfare in the state department of public welfare that administer the program of child welfare services. The problem of convalescent care needs careful consideration with a view to developing satisfactory standards and increased facilities. The effective use of convalescent facilities meeting desirable standards provides a means of reducing hospital sojourn, and at the same time offers an opportunity for a more satisfactory transition from the period of active treatment in a hospital in readjusting a child to his return home.

Cooperation With Professional and Lay Groups.—Perhaps in no other type of service for children is there such a distinct need for a close correlation of all services affecting the program as in work for crippled children. The state agencies are utilizing extensively state and local services of both public and private agencies, and the outstanding work of private organizations and agencies has added much to the development of the program. In every state many valuable contributions are being made to the program by medical, health, nursing, education, welfare, and vocational rehabilitation agencies and organizations. This cooperation with various professional and lay groups is well exemplified in the representation of these groups on general and technical advisory committees which have been appointed by the majority of state agencies. In all states conducting services for crippled children a physician is serving on either the general advisory committee or the technical advisory committee. In 14 states a pediatrician is serving as a member of the technical advisory committee, and the remaining states are being urged to call upon pediatricians for service of this nature as well as for actual participation as consultants and clinic physicians in the program of care for crippled children.

Scope of Program.—No specific definition of "crippled child" was given in the wording of the Social Security Act, although several definitions had been proposed in the hearings before Congress. An investigation of the laws under which state agencies were operating showed variations extending from a very strict definition limiting the services to

children with motor disabilities to a very broad definition and interpretation, which included all physically handicapped children who could be benefited by medical or surgical treatment. The various definitions of a crippled child incorporated in the laws of the several states have been accepted, for the present, with the idea that in actual practice definitions will be broadened gradually to include as wide a range of crippling conditions as is practicable within the limitations of the available funds. A few states have included such conditions as rheumatic heart disease and diabetes, but most of the cases accepted for care have been orthopedic and plastic conditions. As the peak load of children awaiting orthopedic care when the Social Security Act became effective is passed, it is possible that proportionately more care may be given to children crippled from cardiac conditions, especially in those states where rheumatic disease is common. Children whose chief disability is incurable blindness, deafness, or mental defect, and those having abnormalities requiring permanent custodial care are considered beyond the scope of this program.

When the Social Security Act was passed in August, 1935, there were marked differences in the extent and type of programs provided by state agencies. Only twelve states had developed services as broad in scope as those provided under the act. States that started with provision for little except diagnosis and hospitalization have recognized the shortcomings of such a program and have gradually broadened it to include a greater diversity of services. It was to be expected that some state plans in their initial stages would consist almost exclusively of services for physical restoration, but most of these plans are being expanded to provide for case-finding procedures, registration of crippled children, aftercare services and for coordination of health, welfare, nursing, and rehabilitation agencies. There has been observed a growing recognition of the fact that the crippled child needs these supporting services as well as skilled medical care.

Most of the states have taken steps to improve the quality of medical and surgical care and to provide the necessary auxiliary services to make care effective. There is, for instance, need of a continuing effort to bring children under care at an earlier stage, to keep them under continuous treatment and supervision as long as is necessary for their complete physical and social rehabilitation, and to make more readily available the essential aftercare services.

More effective methods for locating crippled children have been put into operation by state agencies during the past year through more systematic reporting by physicians, teachers, nurses, social workers, and others and through the use of epidemiologic reports and birth certificates. The use of epidemiologic reports in locating crippled children at present centers chiefly around the problem of providing prompt care to all needy cases of acute poliomyelitis, but they are also being utilized in a number of states in discovering cases of bone tuberculosis. The reporting of con-

genital defects, such as clubfoot, on the birth certificate is receiving consideration in a number of states. Such reporting is now required by law in six states.

Procedures with regard to acceptance of children for care and planning for care after discharge from the hospital have been reviewed in many states by social workers attached to the state staffs and a number of socially undesirable procedures have been corrected. The problems connected with court commitment are being given careful consideration. Requirements for economic eligibility are being more liberally interpreted so that any crippled child can be accepted for diagnostic service. Decision as to acceptance for treatment and other services following diagnosis is based on the social and economic condition of the family. The generally accepted principle is that no child whose parents are unable to provide adequate treatment from their own resources shall be denied service. Some progress is being made by several states in modifying or discarding certain undesirable requirements such as the signing of a pauper's oath or the signing of an agreement to repay, with interest, the cost of medical care.

A majority of the states have required residence in the state, but many of the official agencies are working out reciprocal relationships with other states for the care of children moving across state lines.

Diagnostic clinic services for crippled children have been greatly extended throughout the country, particularly in rural areas and in areas suffering from severe economic distress. State plans from twenty-seven states which gave information on the number of itinerant clinics scheduled for the fiscal year 1938 indicated that 456 such clinics were to be held during the year. These clinics are in addition to the large number of permanent clinics which are conducted at regular intervals at hospital centers in practically every state.

In 1938, 546 hospitals were approved by forty-eight state and territorial agencies for the care of crippled children. In the main, the special hospitals for crippled children, both public and private, and the general hospitals with orthopedic services located centrally in larger cities care for a majority of the children. There is, however, a trend toward decentralization of hospital services so that the crippled child can be hospitalized in an approved hospital near his own home. Furthermore, the procedures used by state agencies in the authorization of hospitalization and in the issuance of instructions to be carried out on the discharge of a patient have been further improved so that local health and welfare workers are better informed as to the aftercare necessary for good results.

Reports of Service Rendered.—Reports submitted by state agencies on the direct services actually rendered to crippled children have given additional valuable factual data on which to base plans for the future development of state services. The total number of children on the registers

of 43 states, Alaska and Hawaii as of March 31, 1938, was 130,610. Table I presents a picture of certain activities for all the states from which reports were received during the calendar year 1937.

TABLE I

SUMMARY OF CRIPPLED CHILDREN'S SERVICES REPORTS* FOR THE YEAR ENDED DECEMBER 31, 1937

TYPE OF SERVICE	NUMBER
Medical service in clinics (diagnostic or treatment):	
Individuals admitted	77,055
Visits	193,928
Care in hospitals:	
Children under care at beginning of year	3,796
Children admitted to care during year	38,277
Days' care	1,322,750
Care in convalescent homes:	
Children under care at beginning of year	1,337
Children admitted to care during year	3,831
Days' care	380,331
Care in foster homes:	
Children under care at beginning of year	350
Children admitted to care during year	757
Days' care	57,843
Field and office visits by:	
Public health nurses	212,248
Physical therapy technicians	187,250
Medical social workers (January-June)†	47,573
Other social workers (January-June)†	15,797
Individuals admitted by:	
Medical social workers (July-December)†	4,773
Other social workers (July-December)†	4,688
Children referred for vocational rehabilitation	3,654

*Figures are preliminary and incomplete. They represent primarily activities of the official state agencies but include some services provided by other public and private agencies in the various states. They include corrections received in the Children's Bureau through July 31, 1938.

†Owing to revision of report forms, effective July 1, counts of individuals admitted to case work service are available only for last six months of the year.

Unmet Needs.—In spite of the fact that considerable progress has been made in the extension and improvement of state services for crippled children, much remains to be done. If the program is to achieve the intent of the Social Security Act, some means must be found to bring to the attention of the state agency all crippled children. Methods previously employed have been unsuccessful in discovering the child of preschool age who is frequently missed in the school surveys upon which agencies have often depended. In addition to enlisting the interest and assistance of medical, health, nursing, welfare and educational agencies and organizations in reporting crippled children, it is important that some method be developed for informing the general public regarding the services for crippled children that are available and the method by which such services may be obtained. Restrictions imposed by state laws or administrative regulation with respect to residence requirements indicate that if services for crippled children are to be made available to the chil-

dren of families moving across state lines, there is need for further development of reciprocal agreements between states with respect to responsibility for providing such services.

An outstanding need in many state programs appears to be the development of services for general diagnostic medical services and medical supervision of children suffering from orthopedic and plastic defects and from other physical handicapping conditions. In too few states have adequate provisions been made by the state agency for a general physical appraisal and medical supervision by qualified pediatricians of crippled children coming within the state plan of services.

Both convalescent and aftercare services in the child's home have been slower in development than services for physical restoration. The importance of adequate aftercare services following hospitalization cannot be emphasized too strongly. To be most effective, provisions should be made for adequate medical, nursing, physical therapy, and social services.

The facilities for psychometric examinations of crippled children do not appear to be adequate, and in some instances where such facilities are available, they are not being fully utilized. The whole field of mental hygiene with respect to the welfare of the crippled child has scarcely been touched.

Federal and state funds available for crippled children's services at the present time are wholly inadequate for providing diagnostic, treatment, and aftercare services for children suffering from such handicapping conditions as rheumatic fever, rheumatic heart disease, visual defects, and defects of hearing. Greater recognition should be given to the needs of this group as well as to those suffering from orthopedic and plastic defects.

Provisions for the care of the hopelessly crippled child are notably inadequate.

SUMMARY

There has been presented a review of accomplishments in maternal and child health and crippled children's services under the Social Security Act, including a description of administrative procedures, a brief presentation of the programs now being carried out by the states, the qualifications and training of personnel, and methods of cooperation with professional and lay groups.

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FURTHER OBSERVATIONS ON THE METABOLISM AND THE CLINICAL USES OF SODIUM LACTATE

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IN A PREVIOUS communication, Hartmann and Elman[1] reported studies on the effects in dogs of loss of gastrointestinal secretions and demonstrated the therapeutic value of lactate-Ringer's solution* in various types of gastric and intestinal obstruction and fistula and in pancreatic duct fistula. At about the same time Hartmann and Senn[2] submitted data concerning the metabolism of sodium *r*-lactate in the human subject, both in health and in disease, and emphasized particularly the value of sodium *r*-lactate in the treatment of various types of acidosis, and recently Hartmann[3] compared the results in the treatment of diabetic acidosis (1) when no alkali was administered, (2) when *sodium bicarbonate* was used, and (3) when the alkali administration was *sodium lactate,* and emphasized the many ways in which the last mentioned treatment seemed superior to the others.

We now wish to report further observations concerning the metabolism of sodium lactate in the human subject, and its clinical uses in the relief and prevention of acidosis and in rendering the urine alkaline for therapeutic purposes.

I. METABOLISM OF SODIUM LACTATE IN THE NORMAL INDIVIDUAL

PLAN OF STUDY

In an investigation of the fate of intravenously injected sodium lactate in the normal human subject, the general plan of study was as follows: After a rest period of one hour, usually from 7:00 A.M. to 8:00 A.M., the subject's fasting oxygen consumption was determined by use of the Benedict-Roth metabolism apparatus. When two satisfactory tests had been completed, preliminary blood and urine specimens were obtained. On this and subsequent blood samples, serum carbon dioxide content, hydrogen ion concentration, lactic acid, dextrose, inorganic phosphate, and chloride were estimated. The urine samples were analyzed for carbon dioxide content, hydrogen ion concentration, and lactic acid. After the preliminary blood and urine specimens had been collected, the intravenous injection of sodium lactate was started. Five-

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*At times also designated as "combined solution," "Hartmann's solution," and "physiological buffer salts solution."

tenths molar solutions were used, the molar lactate being diluted with an equal volume of distilled water, Ringer's solution, or water containing 0.125 per cent calcium chloride. The calcium chloride was added in an attempt to lessen the discomfort due to tetany which sometimes accompanied the alkalosis developing in the normal subject following sodium lactate administration. The quantity of lactate injected varied from 3.2 to 8.1 c.c. of molar solution per kilogram of body weight, and the injection period ranged from 18 to 27 minutes with the exception of one experiment in which it was 37 minutes. In all of the experiments except the earliest ones, estimation of oxygen consumption was started shortly after the injection had begun and one or two tests of 6 to 7 minutes' duration were made during the injection, another shortly after it was over, then at half-hour intervals for 2 hours, and hourly for one to 3 hours more if the oxygen consumption had not already returned to the basal level. Blood and urine samples were collected immediately after the injection was over and blood again one-half, one, 2, and 3 or 4 hours later. Urine was collected at less frequent intervals until the excretion of lactic acid had become inappreciable.

Seven experiments were carried out with what we believed was racemic sodium lactate prepared from Mallinckrodt's "chemically pure" or "analytical reagent" lactic acid. Recently we were informed that the commercial lactic acid sometimes contains an excess of one isomer, so we may not always have been dealing with a true racemic mixture. Two experiments were carried out with *l*+ lactate, the sarcolactic acid used having been prepared by Peterson and Tatum, of the University of Wisconsin. In addition to the lactate studies, five experiments were carried out in which changes in the oxygen consumption associated with the intravenous injection of 0.5 molar sodium bicarbonate were observed.

RESULTS AND COMMENT

Chemical Changes in General.—The various chemical changes in blood and urine following the lactate injections will not be reported in detail, but Chart 1 gives these findings along with the oxygen consumption data in one representative experiment.

The intravenously injected lactate diffuses rapidly from the blood stream and, except for the portion which is excreted, is completely metabolized in from one to 2 hours. Plasma volume is increased temporarily by dilution, which is to be expected. Blood sugar increases slightly, then sinks to slightly hypoglycemic levels, the rise possibly being explained by a temporary decrease in the amount of dextrose being oxidized in the tissues because of partial substitution by the *d*-lactate as a substrate undergoing oxidation; the latter fall is possibly to be explained by a continuation of the glycogenic mechanism set in motion by the conversion of the *l*+ isomer into liver glycogen. The sodium ion liberated during the oxidation of lactate or its conversion into glycogen

is transported to the kidneys for excretion largely as the bicarbonate salt, so that for several hours after the injection there exists a state of alkalosis of the base bicarbonate excess type with commensurate increase in the hydrogen ion concentration of the blood. Excretion into the urine of the excess base bicarbonate begins almost immediately and soon bicarbonate and the hydrogen ion concentration of the urine reach maximal values (500-600 volumes per cent, and 7.9-8.0, respectively). Within four hours more than one-half of the injected sodium is excreted in this way.

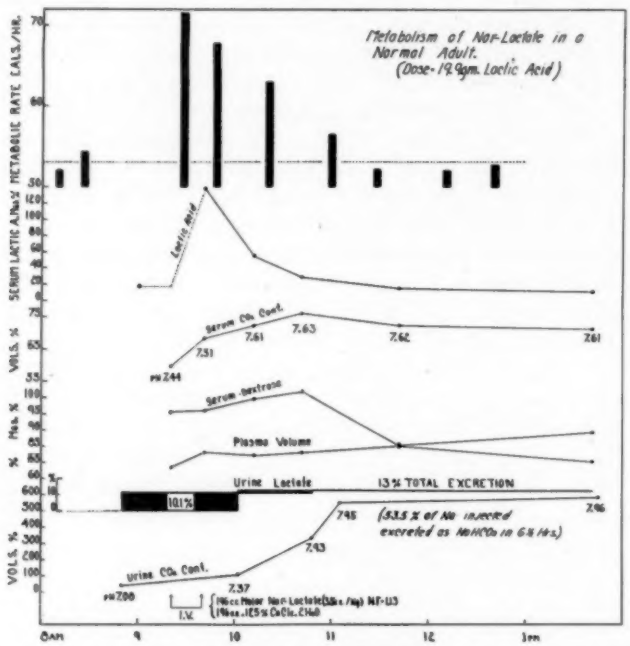

Chart 1.—Chemical changes in blood and urine and changes in oxygen consumption in response to the intravenous injection of sodium *r*-lactate.

Renal Excretion of Injected Lactate.—The quantities of lactic acid excreted in the urine are given in Table I. The small urinary losses of 1.5 per cent and 4.6 per cent of the amounts injected when sodium *l*+ lactate was given are in marked contrast to those of from 12.9 to 14.9 per cent when a corresponding amount of the "racemic mixture" was given. It is true that the injection periods were slightly longer when the *l*+ form was administered, but this difference in the rate of injection is not enough to explain the large differences in the quantities excreted.

Abramson and Eggleton[4] found that following the intravenous injection of sodium *r*-lactate the excreted lactate yielded a zinc salt which analyzed as racemic. Their observation suggests, of course, that the

TABLE I

LACTIC ACID EXCRETION AND CHANGES IN OXYGEN CONSUMPTION FOLLOWING INTRAVENOUS INJECTION OF SODIUM *r*-LACTATE AND SODIUM *l*+ LACTATE

DATE	SUBJECT	INJECTION PERIOD MIN.	M. NA LACTATE C.C. PER KG. BODY WT.	NA LACTATE INJECTED DECIMOLS	LACTIC ACID			PERIOD OF URINARY EXCRETION	BASAL O_2 CONSUMPTION CAL./HR.	EXTRA CAL. ABOVE BASAL	EXTRA CAL. PER DECIMOL NA LACTATE GIVEN
					GIVEN GM.	EXCRETED PER CENT	DISAPPEARED GM.				
1/ 8/32	C. A.	26	7.0(*r*)	4.20	37.8	30.0	26.5	4′21″			
1/20/32	C. A.	37	8.1(*r*)	4.87	43.8	15.6	37.0	2′47″			
1/13/32	A. P.	27	7.2(*r*)	3.30	29.7	29.6	20.9	5′7″			
2/17/32	C. A.	20	3.6(*r*)	2.11	19.0	14.9	16.2	2′33″	62.5	9.1	4.32
6/29/32	A. P.	18	3.5(*r*)	1.60	14.4				46.8	7.7	4.81
2/ 6/32	M. N.	19	3.9(*r*)	2.21	19.9	12.9	10.3	2′26″	53.1	18.2	8.24
6/27/32	M. N.	23	3.4(*r*)	1.90	17.1				53.5	4.4	2.32
2/10/32	C. A.	26	3.2(*l*+)	1.90	17.1	1.4	16.9	2′28″	53.7	16.6	8.74
2/12/32	M. N.	25	3.7(*l*+)	2.08	18.7	4.6	17.8	2′40″	57.8	10.3	4.86

two isomers were utilized equally well. Our finding that considerably less lactate was excreted in the urine after the sodium *l*+ lactate were injected than after a mixture of the two isomers was given, suggests on the other hand, that the *d*- form is utilized less readily than the *l*+ form. If this is the case, it is to be expected that the lactate excreted after the injection of a true racemic mixture would contain an excess of the less readily utilized *d*- isomer.

It will be noted that in two of the three experiments in which as much as 7 c.c. of molar sodium *r*-lactate per kilogram of body weight was given, the lactate excretion continued for a longer period than it did in those in which approximately 3 to 4 c.c. per kilogram were given, and the percentage of the injected lactate lost in the urine was considerably greater, being about 30 per cent of the amount given. This is to be expected because with the larger amounts of lactate a higher level of blood lactic acid was reached. In this connection, it should be remembered that in the normal subject diuresis promptly follows the intravenous injection, which is not always true in dehydrated individuals with acidosis who lose much less lactate in this way.

Changes in Oxygen Consumption During and After the Injection of Lactate and of Bicarbonate.—The data on changes in oxygen consumption are given in Table I and Chart 2. The extra calories burned from the beginning of the intravenous injection until the blood lactic acid had returned to the normal level were computed by plotting the calories per hour obtained in the oxygen consumption determinations against time and tracing with a planimeter, after connecting the points with straight lines, the area representing the calories above the basal level.

The blood lactic acid had usually returned to the normal level within one hour after the injection had started, always within two hours; therefore, in tracing the area of extra calories in the bicarbonate experiments a period of 1½ hours after the injection began was used.

TABLE II

CHANGES IN OXYGEN CONSUMPTION FOLLOWING INTRAVENOUS INJECTION OF SODIUM BICARBONATE

DATE	SUBJECT	MOLAR $NaHCO_3$ GIVEN C.C.	$NaHCO_3$ GIVEN DECIMOLS	$NaHCO_3$ GIVEN GM.	BASAL O_2 CONSUMPTION CAL. PER HR.	EXTRA CAL. ABOVE BASAL	EXTRA CAL. PER DECIMOL $NaHCO_3$ GIVEN
3/ 3/32	C. A.	3.5	2.02	17.0	55.1	11.0	5.45
3/25/32	A. P.	3.5	1.54	12.9	48.6	10.7	6.95
6/24/32	A. P.	3.5	1.54	12.9	45.1	6.4	4.16
3/23/32	M. N.	3.5	1.87	15.7	53.1	8.1	4.49
6/22/32	M. N.	3.5	1.83	15.5	54.1	6.1	3.34

It is apparent from the tables and charts that there was much variation in the extra oxygen consumption per decimol of lactic acid injected in the different experiments in which the sodium *r*-lactate was used. These values varied from 2.32 to 8.24 calories per decimol of sodium lactate given, and it will be noted that the extreme variations were obtained on the same subject. The two experiments with the sodium *l*+ lactate gave 4.86 and 8.74. With sodium bicarbonate the values ranged from 3.34 to 6.95 calories per decimol of alkali given. From the graphs it is obvious also that in several of the experiments with the "racemic" mixture and one with the *l*+ lactate, the oxygen consumption did not return to the basal level by the time the blood lactic acid had returned to normal. When sodium bicarbonate was given, in only one case had the oxygen consumption returned to the basal level within 1½ hours after the injection was started. In one experiment with the "racemic" mixture, subject C. A., February 17, the basal oxygen consumption was considerably higher than on other occasions, but the calories per hour had not fallen even to the basal level of the test day within 3½ hours after the beginning of the injection. In one case in which the *l*+ isomer was given, M. N., February 12, the basal oxygen consumption was also unusually high but fell approximately to the basal level of the preceding and subsequent experiments in slightly over 3 hours after the injection started. If this low level had been used as a base line, the extra calories per decimol of sodium lactate given would have amounted to 8.26 instead of 4.86. In one of the bicarbonate experiments, M. N., June 22, the two estimations of oxygen consumption made during the injection gave values actually slightly lower than the average of the basal oxygen consumption of that day. These low values are in marked contrast to the appreciable increases occurring during the injection in all of the other experiments with both bicarbonate and lactate.

Buchwald, Cori, and Fisher[5] in 1933 published their observations on the influence of intravenously injected *l*+ and *d*– sodium lactate on oxygen consumption in rabbits. When *l*+ lactate was injected the oxida-

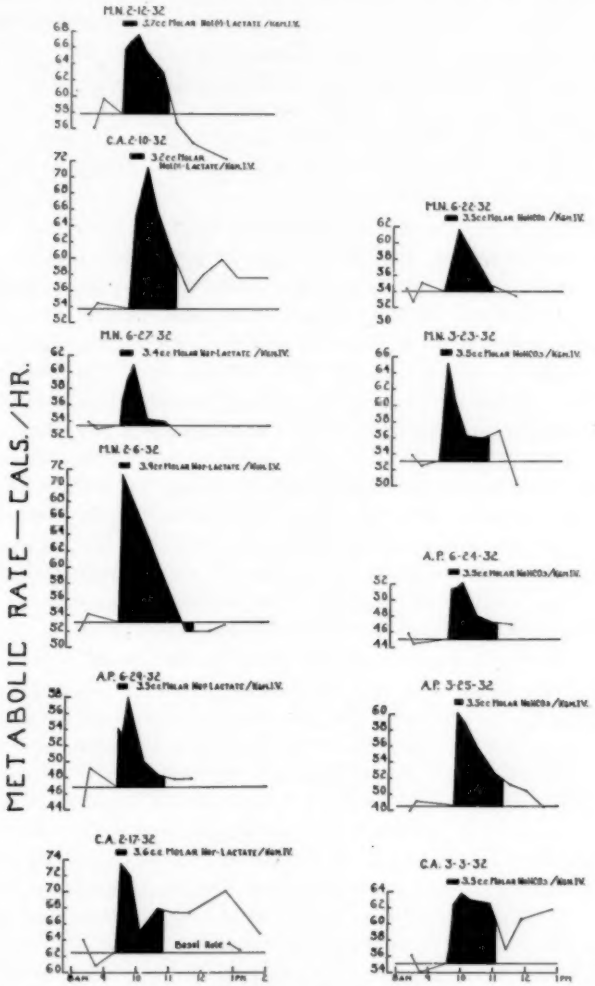

Chart 2.—Changes in oxygen consumption following intravenous injection of sodium *r*-lactate, sodium *l*-lactate, and sodium bicarbonate. The shaded areas include, in the case of the lactate experiments, the period elapsing from the beginning of the injection until the blood lactic acid had reached its normal level; in the case of the bicarbonate experiments, they include a period of one and one-half hours from the time the injection was started.

tion quotients obtained averaged 3.9, varying from 2.6 to 4.5, the extra oxygen consumption accounting for only one-fourth of the lactate which disappeared. They assume that the other three-fourths was converted to

glycogen. Much smaller increases in oxygen consumption were obtained when sodium bicarbonate was injected in equivalent amounts than when sodium lactate was given. When correction was made for the slight bicarbonate effect which did occur, the oxidation quotient became 4.9. Injection of free *l*+ lactic acid which did not involve a bicarbonate error gave an average quotient of 4.4. They observed also that rabbits were able to utilize only one-fourth as much *d*– lactate as *l*+ lactate and the average oxidation quotient when *d*– lactate was given was 1.1. In an earlier investigation Cori and Cori[6] demonstrated glycogen deposition in the liver of rats following the injection of sodium *l*+ lactate but hardly any when *d*– lactate was given.

Abramson, Eggleton, and Eggleton[7] in 1927 reviewed the literature to date on the fate of injected lactate and reported their studies on anesthetized dogs. They did not find sufficient increase in oxygen consumption to account for the lactate which disappeared. The increases in oxygen consumption of 17 to 34 per cent which they obtained after the injection of sodium *r*-lactate they feel are due to the rise in plasma bicarbonate which follows lactate administration, for a similar rise in oxygen consumption occurred when corresponding amounts of bicarbonate were injected. They were unable to demonstrate glycogen synthesis in muscle or liver, and state that they doubt that this occurs in the intact animal, although it has been shown to take place in intact muscle. According to their viewpoint, as pointed out by Buchwald, Cori, and Fisher,[5] injected lactate acts like an easily oxidizable substrate which replaces other food stuffs in metabolism.

It is difficult to evaluate our oxygen consumption data in view of the variations and discrepancies which we have mentioned and in view of the fact that continuous oxygen consumption determinations were not made during the injections. In our experiments, as in those of Abramson and his co-workers, the increases in oxygen consumption when comparable amounts of sodium lactate and sodium bicarbonate were given on the whole did not differ greatly in contrast to the much smaller rises that Buchwald and co-workers obtained with bicarbonate as compared to those with lactate. If it is justifiable to assume that the effect of alkali administration on oxygen consumption is of the same magnitude whether the alkali is given in the form of sodium lactate or of sodium bicarbonate, it is quite apparent that the extra calories following lactate administration are not enough to account for the disappearance of the lactic acid on the assumption that the oxidation quotient of the *l*+ lactate is 4 or 5 and of the *d*– lactate is one. In the experiments in which the sodium *r*-lactate was given, assuming that it was a true racemic mixture and that the excreted lactate was largely the *d*– isomer, the extra oxygen consumption in some cases was not enough to justify the assumption of oxidation quotients of 4 and of one, even if we disregarded the alkali effect. In the two experiments with the *l*+ lactate which, as already

pointed out, were rather unsatisfactory, if we assume an oxidation quotient of 4, the calories left to be considered as due to alkali effect are extremely small. It would seem probable, therefore, that at least part of both the *l*+ and *d*– lactate which disappeared replaced other food stuffs in metabolism.

II. ACIDOSIS OF RENAL ORIGIN

The acidosis of renal insufficiency, when the latter is extreme, seems always to be associated with a combination of phosphate and sulphate retention and loss of fixed base from the body fluids. In cases with less severe renal insufficiency, mild to moderate degrees of acidosis are sometimes encountered in the absence of such changes and seem to be the result of a new electrolyte pattern which is characterized by lower bicarbonate and higher chloride concentrations. It is quite possible that such an altered electrolyte pattern is merely the result of prolonged insufficient alkali intake, relative to its increased excretion with, however, adequate intakes of water and chloride and excessive retention of the latter.

To date (1937, inclusive) we have sixteen examples of this type of acidosis in eleven different infants or children treated with sodium *r*-lactate, in whom follow-up data were secured. The types of renal insufficiency included chronic active hemorrhagic nephritis, both with and without cardiac decompensation, acute and chronic suppurative nephritis, amyloid disease, nephrectomy, and an unusual case of tubular obstruction in an infant. In five instances, edema was present at the time that the acidosis was recognized and treated, and in three dehydration. As may be noted from Table III, in 15 of the 16 instances, the acidosis was relieved satisfactorily: i.e., the observed carbon dioxide content was raised within 12 hours (and usually much sooner) to a normal value, or to one that was in the zone of just mild acidosis (35-45 volumes per cent). In the single exception, a second administration of sodium lactate proved necessary. In comparing the observed rise in carbon dioxide content with that expected on the assumption that all of the sodium lactate is converted into sodium bicarbonate and distributed equally throughout the entire amount of body water (estimated as two-thirds of body weight), a calculation which has previously been described and made use of,[2] the following data are relevant:

Less than expected (–)			More than expected (+)
>20 vol. %	20-10 vol. %	10-0 vol. %	0-10 vol. %
(1) = 6.3%	(3) = 18.7%	(6) = 37.5%	(6) = 37.5%

Average = –5.7 vol. %

It should be mentioned that in the presence of edema, especially when cardiac decompensation is also present, the sodium lactate may be given in hypertonic strength: i.e., as one molar, one-half or one-third molar.

TABLE

RECOVERY FROM ACIDOSIS OF RENAL

No.	Case	Date	Age	Body			Serum†												
							Vols. % CO_2 Content					NaCl	Gm. % Protein			Lactic Acid	Inorg. P.	Ca.	N.P.N.
				Wt. Kg.	Water Liters	Edema	Before	After	Hrs.	Expected	Difference	Mg. %	Total	Alb.	Glob.	Mg. %	Mg. %	Mg. %	Mg. %
1	G- 198	10/24/30	7 yr.	16.9	11.3	0	20.8	51.3	4	43.0	+ 8.3	—	8.50	—	—	12.0	5.0	12.0	87.0
												—	—	—	—	—	—	—	—
2	G- 198	12/15/30	7 yr.	17.0	11.3	0	32.0	46.0	24	44.7	+ 1.3	—	—	—	—	—	—	—	75.0
													—	—	—	—	—	—	—
3	I- 478	3/ 8/32	14 yr.	38.6	25.7	+++	26.0	40.0	6	43.4	− 3.4	—	6.95	1.99	4.96	28.5	8.8	8.8	186.0
												585	—	—	—	—	—	—	—
4	I- 478	4/ 4/32	14 yr.	38.6	25.7	+++	44.9	49.9	22	66.7	−16.8	585	5.65	2.87	2.78	—	7.1	9.1	145.0
													—	—	—	18.0	—	—	—
5	B- 707	5/ 2/32	8 yr.	42.2	27.7	+	28.0	67.5	20	67.7	− 0.2	608	7.60	—	—	—	3.7	—	133.0
													5.00	—	—	—	5.0	—	110.0
6	J-2000	9/ 5/33	8 yr.	25.0	16.7	+	27.0	53.9	15	53.8	+ 0.1	608	7.15	3.90	3.25	—	10.3	—	180.0
													—	—	—	—	—	—	—
7	L- 239	1/23/35	7 yr.	18.0	12.0	Dehyd.	22.3	57.1	12	55.9	+ 1.2	475	5.00	2.90	2.10	—	17.5	7.8	197.0
													—	—	—	—	—	—	215.0
8	E-1663	5/23/35	14 yr.	28.0	18.7	?	15.4	39.5	8	51.4	−11.9	590	6.10	—	—	—	20.0	8.1	135.0
													5.32	1.66	3.66	28.0	19.7	7.5	125.0
9	L-2539	11/18/35	18 da.	2.5	1.7	Dehyd.	22.0	30.0	19	61.6	−31.6	708	—	—	—	—	—	—	—
													—	—	—	—	8.6	—	152.0
10	L-2539	11/19/35	19 da.	2.5	1.7	0	30.0	70.0	34	69.6	+ 0.8	725	—	—	—	—	—	—	100.0
													—	—	—	—	8.0	—	134.0
11	J- 201	10/26/36	7 yr.	20.0	13.3	Dehyd.	15.0	76.4	23	81.2	− 4.8	603	5.44	—	—	—	9.7	—	110.0
													—	—	—	—	—	—	—
12	M- 830	2/25/37	3 yr.	12.2	8.1	++	21.0	55.9	14	62.9	− 6.6	634	—	—	—	—	—	—	93.0
													3.93	1.00	2.93	—	6.5	6.6	56.0
13	M- 830	3/ 2/37	3 yr.	13.2	8.8	++	31.0	58.2	6	64.5	− 6.3	595	—	—	—	—	—	—	49.0
													—	—	—	—	—	—	60.0
14	N- 487	3/21/37	5 mo.	5.3	3.5	0	9.0	25.0	6	41.0	−16.0	351	—	—	—	—	—	—	—
													—	—	—	—	—	—	247.0
15	N- 487	3/22/37	5 mo.	5.3	3.5	0	25.0	50.0	16	57.0	− 7.0	351	—	—	—	—	—	—	—
													—	—	—	—	8.0	5.8	261.0
16	K- 508	7/12/37	7 yr.	16.0	10.7	++	11.2	46.4	9	44.6	+ 1.8	548	4.42	2.36	2.06	—	4.5	5.1	140.0
													5.01	2.12	2.89	—	4.5	5.2	112.0

*M. = Molar concentration.
I.V. = Intravenously.
I.P. = Intraperitoneally.
H. = Subcutaneously.
R. = Ringer's solution.
F.L.R. = Fortified Lactate-Ringer's solution.
D. = Died—No autopsy.
A. = Autopsy.
I. = Improved and still living.

†When double figures are given, the lower denote determinations after treatment.

In addition to these 15 instances in which follow-up data were secured, there have been many more occasions of apparently satisfactory relief, as judged by the amelioration of clinical symptoms of acidosis. Once, following the removal of most of the single remaining kidney in a child with chronic suppurative nephritis, the occurrence of acidosis was prevented for a period of almost a month by frequent administrations of sodium lactate solution. In the case with chronic amyloid disease (Case 8, Table III), as well as in Cases 1 and 2, recurrences of acidosis were frequent, and for a period of months were relieved by lactate administration.

It should also be mentioned that in three adults, the acidosis which followed prostatectomy and postoperative oliguria, vomiting, and dehy-

III

INSUFFICIENCY AFTER NA R-LACTATE THERAPY

Na r-Lactate*			Ringer's	Dextrose		Diagnosis — Remarks	Outcome
	Molar						
	cc.	cc./Kg.	cc./Kg.	cc.	%		
112 cc. M.+225 cc. R. I.V.	112.0	6.6	13.3	—	—	Chronic suppurative nephritis (pyonephrosis).	
64 cc. M.+50 cc. R. I.V.	64.0	3.8	2.9	—	—		D. 6/ 5/31
200 cc. M. I.V.	200.0	5.1	—	—	—	Nephrotic stage of hemorrhagic nephritis and cardiac decompensation.	A. 4/ 7/32
250 cc. M.+50 cc. R. I.V.	250.0	6.4	1.3	—	—		
3000 cc. ⅙ M. I.V.+H.	500.0	11.8	—	300 I.V.	20	Anuria following removal of tuberculous kidney.	D. 6/27/32
400 cc. M. I.V.+600 cc. ⅙ M. H.	200.0	8.0	—	250 I.V.	20	Hem. neph. approaching terminal stage.	I.
1080 cc. F.L.R. I.V.+I.P.+H.	80.0	4.4	40.0	250 I.V.	10	Subacute hem. neph.	D. 1/25/35
1500 cc. F.L.R. I.V.+H.	300.0	10.7	42.9	—	—	Amyloidosis—chr. staph. suppuration.	A. 6/16/35
180 cc. ⅙ M. I.V.+H.	30.0	12.0	80.0	—	—	Multiple staph. abscesses of kidneys.	
180 cc. ⅙ M. I.V.+H.	30.0	12.0	—	—	—		A. 12/ 3/35
2400 cc. ⅙ M. I.V.+H.	400.0	20.0	80.0	—	—	Chr. suppurative neph.	A. 12/ 1/36
900 cc. F.L.R. I.V.+H.	150.0	12.3	92.0	150 I.V.	10	Nephrotic stage of chr. hem. neph.	
780 ⅙ M. I.V.+H.	130.0	9.8	—	—	—		I.
300 cc. F.L.R. I.V.+H.	50.0	9.4	37.7	—	—	Oliguria—tubules filled and obstructed by precipitated material of undetermined composition.	A. 3/24/37
300 cc. F.L.R. I.V.+H.	50.0	9.4	37.7	—	—		
960 cc. ⅙ M. I.V.+H.	160.0	10.0	—	—	—	Hem. neph. approaching terminal stage.	I.

dration, was also relieved satisfactorily by this method. Satisfactory results were also secured in two adults who had developed acidosis following the development of anuria after transfusion reactions, and in one adult who had been given a fatal dose of diethylene glycol containing sulfanilamide ("Elixir of Sulfanilamide") and who had developed severe acidosis following almost complete suppression of urine.

In the chronic type of renal insufficiency when vomiting is absent or negligible, the continued oral administration of sodium lactate may be quite efficacious in relieving acidosis and preventing its recurrence. For this purpose, amounts of sodium lactate varying from 50 to 150 c.c. (1-5 c.c. of molar solution per kilogram) may have to be administered daily in three or four divided doses.

TABLE

RECOVERY OF ACIDOSIS OF DIARRHEAL ORIGIN

No.	Case	Date	Age	Body			Serum*												
							Vols. %		CO_2 Content			NaCl	Gm. % Protein			Lactic Acid	Inorg. P.	Ca.	N.P.N.
				Wt. Kg.	Water Liters	Edema	Before	After	Hrs.	Expected	Difference	Mg. %	Total	Alb.	Glob.	Mg. %	Mg. %	Mg. %	Mg. %
1	G-1608	8/10/30	6 mo.	6.6	4.4		37.7	45.0	2	47.6	−2.6	509 573							
2	G-2352	11/22/30	6 wk.	2.7	1.8		26.9	46.3	½	51.7	−5.4								
3	H- 479	2/28/31	8 mo.	6.3	4.2		23.6	46.5	3½	55.6	−9.1								
4	H- 669	3/14/31	5 wk.	2.7	1.8		23.9	48.3	3	61.2	−12.9								
5	H-1652	7/19/31	3 mo.	5.0	3.3		13.0	48.0	5½	40.1	+ 7.9								
6	H-2202	9/22/31	2 mo.	3.0	2.0		31.9	43.1	18	43.1	0	672 675	7.43				5.5		58.5
7	H-2641	11/27/31	8 mo.	7.6	5.0		27.4	69.5	14	67.7	+ 1.8	596 630 602	6.13				3.15		19.0
8	I-1728	9/15/32	16 da.	3.1	2.0		30.7	42.9	2½	69.8	−16.9								
9	I-1760	9/ 2/32	7 wk.	3.3	2.2		17.4	37.8	5	58.1	−20.4								
10	J- 219	1/23/33	6 mo.	6.5	4.3		23.7	41.6	3	58.3	−16.7	872 655	7.00 4.47			63.5 98.6 26.8			127.0 34.0
11	J-1574	7/22/33	9 mo.	5.2	3.5		28.0	72.0	15	70.2	+ 1.8	661 596						10.0	
12	J-3009	9/ 5/33	7 mo.	5.0	3.3		36.8	52.5	14	77.5	−25.0								
13	J-2168	9/26/33	6 wk.	3.1	2.1		16.5	61.8	10	59.2	− 2.6	665 667	9.05 5.61						120.0 47.0
14	J-2350	10/18/33	5 mo.	4.3	2.9		37.0	53.3	11½	44.9	+ 3.4	608 567	8.74 5.67			49.8			47.0 20.8
15	J-2292	11/ 7/33	5 wk.	2.8	1.9		23.1	48.5	13	43.1	+ 5.4	678	6.95						33.0 28.0
16	J-2713	12/10/33	2 mo.	3.5	2.3		30.2	53.4	15	49.6	+ 3.8	745	7.95			40.9			60.0
17	L- 377	2/15/34	10 mo.	8.8	5.9		33.6	58.7	4½	55.6	+ 3.1	748 655	7.95 6.83						45.0 48.0
18	K-2378	10/29/34	11 da.	3.3	2.2		17.2	36.8	24	47.7	−10.9	725					4.7	11.9	32.0
19	K-2264	10/24/34	16 da.	2.6	1.7		16.2	43.2	22	55.7	−12.5	700	9.18			40.6	7.2		103.0
20	K-2432	11/ 5/34	7 mo.	6.5	4.1		37.5	74.1	24	73.0	+ 1.1		5.35						40.0
21	K-2730	1/15/35	4 wk.	2.9	1.9		20.0	26.0	2½	55.3	−29.3	785							53.5
22	K-2730	1/15/35	4 wk.	2.9	1.9		26.0	32.0	2¼	61.3	−29.3	765							53.5
23	L- 116	1/18/35	1 mo.	2.8	1.9		12.9	46.3	20	43.5	+ 2.8	675	6.03						30.0
24	L- 303	1/23/35	7 mo.	5.8	3.9		19.1	24.6	7	78.3	−53.7	715							
25	L- 327	2/ 8/35	5 mo.	5.9	3.9		18.0	56.3	9	55.3	+ 1.0	503 643	4.96						22.0
26	L- 687	4/ 3/35	6 wk.	3.8	2.5		19.0	40.7	16	37.0	+ 3.7		5.60			28.7	5.0	9.0	52.0
27	L- 995	5/21/35	5 mo.	5.4	3.6		17.0	71.0	29	79.2	− 8.2	705	8.70 7.30			21.5 72.4			217.0 204.0

*When double figures are given, the lower denote determinations after treatment.

†M. = Molar concentration.
I.V. = Intravenously.
I.P. = Intraperitoneally.
H. = Subcutaneously.
C.I.V. = Continuous intravenous.
R. = Ringer's solution.
F.L.R. = Fortified Lactate-Ringer's solution.
D. = Died—No autopsy.
A. = Autopsy.
I. = Improved and still living.

IV

AFTER NA R-LACTATE—NONSPECIFIC DIARRHEA

Na r-Lactate†			Ringer's	Dextrose		Diagnosis — Remarks	Outcome
	Molar						
	cc.	cc./Kg.	cc./Kg.	cc.	%		
20 cc. M.+130 cc. R.+100 cc. 10% dextrose I.V.	20.0	3.0	20.0	150	10	Convulsions, circulatory failure—moribund at time of treatment.	A. 8/10/30
20 cc. M.+400 cc. R. I.V.	20.0	7.4	148.0	40 80	5 10	B. coli septicemia, otitis media, broncho-pneumonia.	D. 12/ 4/30
60 cc. M.+100 cc. 5% dextrose I.V.	60.0	9.5		100	5	Mastoiditis, broncho-pneumonia, necrosis of colon.	A. 3/ 1/31
30 cc. M.+50 cc. 20% dextrose I.V.	30.0	11.1	129.0	50	20	Athrepsia, thrombosis of longitudinal sinus, circulatory collapse.	A. 3/16/31
40 cc. M.+205 cc. 5% dextrose I.V.	40.0	8.0	50.0	205	5	Broncho-pneumonia, moribund at time of treatment.	A. 7/21/31
10 cc. M.+300 cc. R. I.P.	10.0	3.3	100.0			Otitis media, broncho-pneumonia, circulatory collapse.	D. 10/ 6/31
30 cc. M.+60 cc. dextrose I.V. 60 cc. M.+R.+D. C. I.V.	90.0	11.8	110.0	860	10	Otitis media, mastoiditis—continuous I.V. drip for 31 hrs.; equal parts 10% dextrose and lactate Ringer's.	I.
210 cc. ⅙ M. I.V.+I.P.	35.0	11.2	241.0			Spina bifida, hydrocephalus, otitis media, broncho-pneumonia.	A. 9/17/32
20 cc. M.+100 cc. R. I.V. 20 cc. M.+100 cc. R. H.	40.0	12.1	61.0			Spina bifida, hydrocephalus, otitis media, sclerema.	A. 9/ 8/32
180 cc. ⅙ M. I.V. 220 cc. ⅙ M. H.+I. P.	66.0	10.1	62.0			Nutritional edema, convulsions.	I.
400 cc. ⅙ M. I.P.	66.0	12.6	77.0			Carpopedal spasm, cardiac dilatation.	A. 7/24/33
360 cc. ⅙ M. I.P.	60.0	12.0	80.0	200	10	Pertussis, meningismus, circulatory collapse.	A. 9/ 6/33
240 cc. ⅙ M. I.V.	40.0	12.9	258.0	238 C. I. V.	10	Otitis media, 10% Dextrose for 58 hrs. by continuous intravenous drip.	I.
10 cc. M.+283 cc. R.+282 cc. 10% Dextrose	10.0	2.1	66.0	282	10	Otitis media.	I.
100 cc. ⅙ M. I.V.	16.0	6.0	30.0			Otitis media, mastoiditis, ulcerative enteritis.	A. 11/17/33
120 cc. ⅙ M. I.V.	20.0	5.7	228.0			Otitis media.	I.
120 cc. ⅙ M. I.V. 150 cc. ⅙ M. I.P. 80 cc. ⅙ M. H.	58.0	6.5	47.0			Otitis media.	I.
180 cc. ⅙ M. H.	30.0	9.0	38.0	125	5		I.
90 cc. ⅙ M. I.V. 90 cc. ⅙ M. H.	30.0	11.5	46.0	60	10	Broncho-pneumonia, thrombosis renal vein.	A. 10/15/34
195 cc. ⅙ M. I.V. 195 cc. ⅙ M. H.	65.0	10.0	101.0	140	20	Pharyngitis, pyelitis, mental deficiency.	I.
180 cc. ⅙ M. H.+I.P.	30.0	10.3				Birth injury, cyanosis, convulsions, otitis media.	I.
60 cc. ⅙ M. I.V. 120 cc. ⅙ M. H.	30.0	10.3					I.
35 cc. ⅙ M. I.V. 120 cc. ⅙ M. I.V.+H.	26.0	9.2	153.0	80	20	Cyanosis, circulatory collapse.	I.
450 cc. 1/5 M. H.+I.P.	103.0	17.7		100	10	Congenital heart disease, broncho-pneumonia, mental deficiency.	D. 1/23/35
5 cc. M.+120 cc. R.+120 cc. 10% Dextrose I.V. 360cc. ⅙M.H.+I.P.	65.0	11.0	20.0	120	10	Broncho-pneumonia, staphylococcus septicemia, moribund at time of treatment.	A. 2/19/35
20 cc. M.+100 cc. 10% Dextrose I.V.	20.0	5.2	26.0	100	10	Degeneration of cerebral cortex, convulsions, broncho-pneumonia.	A. 4/ 8/35
100 cc. M.+750 cc. R. I.V.+H.+I.P.	100.0	18.5	138.0	300	10	Thrombosis transverse sinus, meningitis, broncho-pneumonia.	A. 5/23/35

TABLE IV—

RECOVERY OF ACIDOSIS OF DIARRHEAL ORIGIN

No.	Case	Date	Age	Body			Serum*												
							Vols. %		CO_2 Content			NaCl	Gm. % Protein			Lactic Acid	Inorg. P.	Ca.	N.P.N.
				Wt. Kg.	Water Liters	Edema	Before	After	Hrs.	Expected	Difference	Mg. %	Total	Alb.	Glob.	Mg. %	Mg. %	Mg. %	Mg. %
28	L-1394	7/11/35	11 da.	3.1	2.1		27.9	56.6	19	59.9	− 4.3								
29	L-1406	7/12/35	3 wk.	2.7	1.8		14.8	58.0	12	114.3	−56.3								
30	L-1511	7/26/35	4 wk.	2.5	1.7		24.1	56.0	24	50.4	+ 5.6								113.0 60.0
31	L-1522	7/28/35	2 wk.	3.1	2.1		12.0	55.0	21½	54.6	+ 0.4					44.1 60.5			
32	L-1554	8/ 1/35	2 wk.	2.2	1.5		12.9	30.1	13	42.7	−12.6								
33	L-1564	8/ 2/35	2 wk.	2.1	1.4		22.9	39.8	20	86.9	−47.1								
34	L-2600	12/ /35	6 wk.	3.1	2.1		17.0	46.2	5	59.6	−13.4								
35	M- 137	1/ 7/36	8 mo.	5.4	3.6		22.0	42.4	14	50.6	− 8.2	650	6.19						29.0
36	L-2448	1/ 9/36	3 mo.	3.7	2.5		18.0	49.8	30	63.6	−13.8	579	7.30				9.3	7.5	26.5 31.5
37	M- 155	1/10/36	14 mo.	8.3	5.5		20.5	43.5	5	53.0	− 9.5						4.0	10.2	
38	M- 188	1/15/36	20 mo.	13.0	8.6		28.9	52.1	17	46.7	+ 5.4								
39	M- 663	4/30/36	3 wk.	2.6	1.7		21.2	48.1	5½	60.7	−12.6								47.0 35.5
40	M-1789	9/21/36	2 mo.	4.2	2.8		20.0	50.6	12	52.0	− 1.4								
41	M-2061	11/15/36	9 mo.	4.9	3.3		32.0	39.5		65.9	−26.4						3.1	9.2	20.0
42	L-2210	11/15/36	3 mo.	3.0	2.0		13.1	33.7	12	50.0	−16.3	854 790	7.03						66.0 74.0
43	N- 525	3/29/37	8 da.	2.0	1.3		17.4	44.0	20	101.8	−57.8								
44	N- 595	4/11/37	3 wk.	1.9	1.2		9.5	22.5	2½	65.5	−43.0								

TABLE

CASES OF

No.	Case	Date	Age	Body			Serum												
							Vols. %		CO_2 Content			NaCl	Gm. % Protein			Lactic Acid	Inorg. P.	Ca.	N.P.N.
				Wt. Kg.	Water Liters	Edema	Before	After	Hrs.	Expected	Difference	Mg. %	Total	Alb.	Glob.	Mg. %	Mg. %	Mg. %	Mg. %
1	G-1683	8/20/30	3 yr.				25.0	66.4											
2	G-2058	10/28/30	16 mo.	7.2	4.8		27.5	44.6	3	69.5	−24.9								
3	L-1431	7/16/35	2 yr.	11.4	7.6		31.5	54.5	13	50.6	+ 3.9								
4	L-1859	9/ 8/35	5 yr.	17.0	11.3		30.0	61.0	12	63.6	− 2.6								
5	L-2455	10/30/35	10 mo.	8.8	5.9		15.0	63.4	21	66.2	− 2.8								
6	M-1253	7/11/36	2 yr.	11.0	7.3		10.0	78.0	14	56.0	+22.0								
7	M-1411	8/ 1/36	5 mo.	4.7	3.1		12.0	16.0	13	55.3	−39.3								
8	N-1126	7/ 1/37	18 mo.	7.9	5.2		38.0	44.6	7	72.4	−27.8								

*When double figures are given, the lower denote determinations after treatment.

†M. = Molar concentration.
I.V. = Intravenously.
I.P. = Intraperitoneally.
H. = Subcutaneously.
C.I.V. — Continuous Intravenous
R. = Ringer's solution.
F.L.R. = Fortified Lactate-Ringer's solution
D. = Died—No Autopsy.
A. = Autopsy.
L. = Improved and still living.

CONT'D.

AFTER Na r-LACTATE—NONSPECIFIC DIARRHEA

Na r-Lactate†			Ringer's	Dextrose		Diagnosis — Remarks	Outcome
	Molar						
	CC.	CC./Kg.	CC./Kg.	CC.	%		
60 cc. ⅙ M. I.V. 20 cc. M.+400 cc. R. H.	30.0	9.6	129.0	75	10	Streptococcus and B. coli septicemia.	A. 8/ 4/35
70 cc. M.+550 cc. R. I.V.+H.	80.0	29.6	333.0	75	10	Cellulitis, septicemia, moribund at time of treatment.	A. 7/14/35
20 cc. M.+200 cc. R. H.	20.0	8.0	80.0	65	10	Impetigo, moribund at time of treatment.	A. 8/ 1/35
40 cc. M.+380 cc. R. I.V.+H.	40.0	12.9	122.0			Comatose at time of treatment.	I.
120 cc. ⅙ M. I.V.+I.P.	20.0	9.0	45.0	50	10	Prematurity.	D. 8/ 2/35
240 cc. ⅙ M. I.V.+H.	40.0	19.0	87.0	60	10	Otitis media—moribund at time of treatment.	A. 8/16/35
280 cc. ⅙ M. I.V.+H.	40.0	12.8	80.0	50	10	Otitis media.	I.
275 cc. ⅙ M. I.V.+H.	46.0	8.5	37.0			Otitis media, rickets.	I.
300 cc. ⅙ M. I.V.+H.	51.0	13.8	54.0			Impetigo, broncho-pneumonia, otitis media, convulsions.	A. 1/19/36
480 cc. ⅙ M. I.V.+H.	80.0	9.6	39.0	100	10	Spastic paralysis, otitis media, rickets.	I.
420 cc. ⅙ M. H.	70.0	5.4	31.0	150	10	Otitis media, ketosis.	I.
180 cc. ⅙ M. I.V.+H.	30.0	11.5	153.0	70	10	Otitis media, thrush.	I.
40 cc. M.+400 cc. R. I.V.+H.	40.0	9.5	95.0	80	10	Otitis media.	I.
50 cc. M.+250 cc. R. I.V.+I.P.	50.0	10.2	81.0			Athrepsia, otitis media, broncho-pneumonia.	I.
200 cc. ⅙ M. I.P.	33.0	11.0	133.0	70	10	Impetigo, otitis media, broncho-pneumonia.	A. 11/17/36
30 cc. M.+360 cc. R. I.V.+H. 19 cc. M.+75 cc. 5% Dextrose H.	49.0	24.5	180.0	75	5	Prematurity, peritonitis, broncho-pneumonia, circulatory collapse.	A. 3/ 3/37
180 ⅙ M. I.V.+P.	30.0	15.7	210.0			Moribund at time of treatment.	D. 4/14/38

IV-A

BACILLARY DYSENTERY

Na r-Lactate			Ringer's	Dextrose		Diagnosis — Remarks	Outcome
	Molar						
	CC.	CC./Kg.	CC./Kg.	CC.	%		
40 cc. M.+1700 cc. R. H. 20 cc. M.+200 cc. Dextrose I.V.	60.0			400	10	Cellulitis, hemolytic streptococcus septicemia.	A. 8/28/30
360 cc. ¼ M. H.	90.0	12.5				Hiss-Russell, hemolytic streptococcus septicemia, otitis media, mastoiditis, pyuria.	D. 10/28/30
65 cc. M.+800 cc. R. I.V.+H.	65.0	5.7	70.0	250	10	Hiss-Russell, parotitis.	I.
1020 cc. ⅙ M. I.V.+H.	170.0	10.0	40.0	250	10	Hiss-Russell.	I.
810 cc. ⅙ M. I.V.+H.+I.P.	135.0	15.3	51.0	115	10	Hiss-Russell, scarlet fever, septicemia, meningitis, peritonitis.	D. 12/13/35
660 ⅙ M. I.V.+H.	150.0	13.6	73.0	100	10	Hiss-Russell, acute parotitis.	I.
360 cc. ⅙ M. I.V.+H.	60.0	12.8	85.0	100	10	Shiga, sclerema, moribund at time of treatment.	D. 8/ 2/36
480 cc. ⅙ M. I.V.+H.	80.0	10.0	40.0	100	10	Hiss-Russell, otitis media, encephalitis.	A. 7/ 4/37

III. ACIDOSIS OF DIARRHEAL ORIGIN

This form of acidosis, compared with that of renal origin, is somewhat more complex in that contributory factors are: (1) loss of base bicarbonate from the body as the result of failure to reabsorb alkaline digestive juices; (2) renal insufficiency due partly merely to oliguria, the result of anhydremia, and partly also to acute degenerative renal changes; (3) circulatory failure, particularly the result of anhydremia which leads to tissue anoxia and permits such acids as lactic acid to accumulate, and (4) ketosis, the result of starvation or infection, seen especially when the diarrhea is the result of acute ileocolitis due to the dysentery bacillus.

As in a previous communication,[8] we prefer to classify the acute diarrheas under two main types: (1) the so-called nonspecific diarrhea, and (2) acute bacillary dysentery. As may be noted from Tables IV and IV-A, we now (inclusive of 1937) have 60 cases of acidosis associated with nonspecific diarrhea treated with sodium lactate solution, and 8 due to acute bacillary dysentery, in whom follow-up data have been secured. It may also be noted that all but 3 were satisfactorily relieved. In addition, we have treated apparently successfully, but without confirmatory follow-up laboratory data, 100 more cases of acidosis associated with nonspecific diarrhea and 41 with acute bacillary dysentery. The initial carbon dioxide contents in these cases without follow-up data varied from 10 to 39 volumes per cent, and 44 were under 28 volumes per cent. In comparing the observed effects in 64 cases with the calculated, the following data are of interest:

Less than expected (−)				More than expected (+)	
>30 vol. %	30-20 vol. %	20-10 vol. %	10-0 vol. %	0-10 vol. %	10 vol. %
(7) = 10.9%	(8) = 12.5%	(16) = 25.0%	(17) = 26.5%	(15) = 23.5%	(1) = 1.6%

Average = −11.8 vol. %

It should be mentioned that the success in the relief of acidosis in such cases was much better than the success of treatment as a whole. The eventual mortality in this group of patients was 51 per cent. In many instances the patients were moribund at the time of admission to the hospital, but despite their moribund state they metabolized sodium lactate fairly normally and were completely relieved of acidosis before death. It should also be mentioned that in this type of case there is a strong tendency for recurrence of acidosis, and lactate-Ringer's solution has to be given after the initial relief of acidosis in amounts sufficient to prevent recurrence of dehydration if recurrence of acidosis is to be avoided. Such fluid administration may be given with interrupted in-

jections subcutaneously, intraperitoneally or intravenously in the usual amounts, or as a continuous intravenous drip.

IV. DIABETIC ACIDOSIS

Inclusive of 1937 we have treated 55 cases of diabetic acidosis with sodium lactate, and in Chart 3 and Table V the results of treatment are

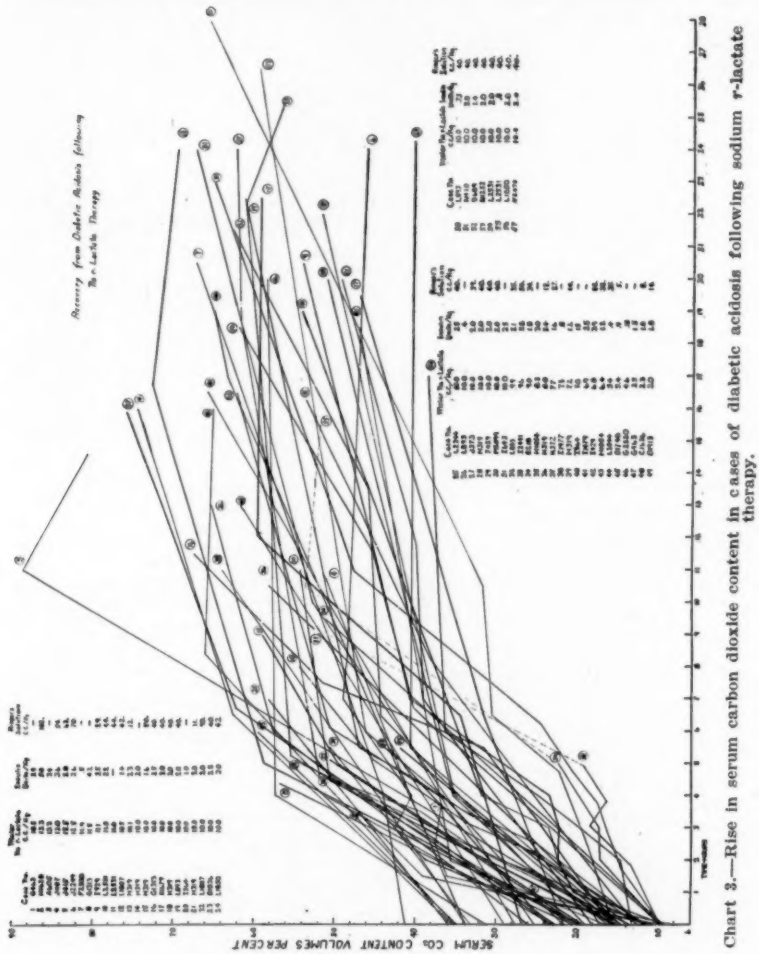

Chart 3.—Rise in serum carbon dioxide content in cases of diabetic acidosis following sodium r-lactate therapy.

indicated. It will be noted that of these 55 cases only 2 were unsatisfactory by definition, and in only one case did the carbon dioxide content rise to more than 80 volumes per cent after the successful relief of acidosis. Furthermore, only two deaths occurred in the group, a mortality of 3.6 per cent.

TABLE V

Data Incident to Recovery from Acidosis of Diabetic Origin After Na r-Lactate Therapy

				Serum															Therapy				
				Body		CO_2 Content—Vols. %														Molar			
No.	Case	Date	Age	Wt. Kg.	H_2O Liter (Estimated)	Before	After	Hrs.	Expected	Difference	Nacl. Mg. %	Protein G.%	Alb. G.%	Glob. G.%	Lactic Acid Mg. %	Inorg. P. Mg. %	N.P.N. Mg. %	Dextrose Mg. %	Na r-Lactate*	CC.	CC./Kg.	Ringer's Solution CC./Kg.	Insulin 1st 8 Hrs. U./Kg.
1	G- 463	12/28/30	11 yr.	35.0	23.3	8.5	36.0 37.6 36.8	2 3 4	71.0	−35.0 −33.4 −34.2	660 655 669	10.5 6.68 5.95 5.29			100.8 75.6 55.0	5.7 1.4 1.0	47.0 55.0 45.0 53.0	432 407 498 131		650	18.5	—	2.9
2	H-1628	7/14/31	6 yr.	15.0	10.0	10.8	39.0 47.0	1¾ 3½	55.6	−16.6 − 8.6								560 360 296	200 cc. M.+ 200 cc. R. I.V.	200	13.3	102	5.0
3	A- 605	5/30/33	21 yr.	44.0	29.3	14.4	88.7 80.9 70.4	11 14½ 36	58.9	+29.8 +22.0 +11.5	562 468 456 520	10.7 7.05					49.0 38.8	588 29 250 397	1350 ⅙ M. I.V. 2150 ⅙ M. (H.)	583	13.2	—	2.4
4	J-1187	6/12/33	11 mo.	5.7	3.8	15.0	39.0 52.0	3 11	59.2	−20.2 − 7.2								300 172 58	75 cc. M.+375 cc. H_2O-½ I.V. ½ H.	75	13.0	54	3.6
5	J- 415	2/23/33	8 mo.	4.6	3.1	12.8	24.5 38.3 53.9	4 8 16	55.0	−30.5 −16.7 − 1.1	696	9.02			32.2 49.7 33.8	4.7	37.5	628 645 312 75	120 cc. ⅙ M. I.V. 220 cc. ⅙ M. (H.)	58.3	12.5	62	2.8
6	J-2249	10/ 6/33	2¼ yr.	11.3	7.5	10.4	29.2 38.6 42.5 40.4 49.0 46.4	1½ 2½ 3½ 4½ 7½ 24	52.6	−23.4 −14.0 −10.1 −12.2 − 3.6 − 6.2	596	8.72 7.48 7.02 7.65 7.56			32.8 58.0 35.2 26.5 20.2		25.0 25.0 25.0 25.0 25.0	525 237 115 56 48 56		141	12.5	70	2.6
7	F-2500	4/ 4/33	7 yr.	21.0	14.0	41.2	44.0 67.3	6 20½	81.2	−37.2 −13.9							69.7	176 109 162	1500 cc. ⅙ M. I.V.—H.	250	11.9	—	0.5
8	G-1313	7/ 7/30	13 yr.	9.6	6.4	20.3	29.0 56.9	1½ 4½	58.7	−29.7 − 1.8	521				26.4 34.0		22.0	410 508 335		110	11.5	—	4.2

9	I- 929	5/12/32	14 yr.	27.0	18.0	11.4	20.3 22.2 22.1 23.5 40.7 54.0	2½ 3½ 4½ 6 8½ 20½	48.7	−28.4 −26.5 −26.6 −25.2 − 8.0 + 5.3	595 544	6.70 6.35 5.42					32.0	360 263 195 168 150 133	200 cc. ⅙ M. I.V. 800 cc. ⅙ M. I.P. 800 cc. ⅙ M. (H.)	300	11.1	29	2.5
10	L-2531	3/30/36	6½ yr.	18.1	12.0	9.7	13.5	2	47.0	−33.5	658 615	10.4			27.7 83.4		27.0	405 266	200 M.+1000 cc. H_2O −I.V.+H.	200	11.0	44	2.2
11	L-2531	3/30/36	6½ yr.	18.1	12.0	19.1	18.2 16.3 52.8 52.8	3 3¾ 5 9¼ 22	56.4	−28.8 −30.7 − 3.6 − 3.6	623 603 612 527 533	 8.75 7.65			 41.6 33.0 32.2		 20.0 17.0	199 166 113 284	200 M.+1000 cc. H_2O I.V.+H.	200	11.0	44	—
12	L-1807	8/ 5/36	5 yr.	19.0	12.6	19.8 pH. 700	58.5 72.8 69.9	5 17 24	55.4	+ 3.1 +17.4 +14.5								290 250 55 80	200 cc. M.+1000 cc. H_2O I.V.+H.	200	10.5	42	1.4
13	H- 319	2/ 2/34	12 yr.	32.6	21.7	19.0	 49.8 59.0	 5 9	53.0	 − 3.2 + 6.0					54.8 40.2 18.9			775 292 181	1980 cc. ⅙ M. Continuous Drip	330	10.1	12	2.3
14	H- 319	12/26/33	12 yr.	32.0	21.3	35.5	62.5 74.7	6½ 16	69.2	− 6.7 + 5.5	515 486	10.2			38.9 30.8 21.4		48.0 52.0	492 197 60	960−⅙ M. I.V. 960−⅙ M. H.	320	10.0	—	2.0
15	H- 319	3/19/34	12 yr.	31.0	20.6	26.7	34.1 59.8 59.6	6½ 12 22½	60.4	−26.3 − 0.6 − 0.8					27.7 64.3 23.9 29.9			525 347 184 98	310 cc. M.+1550 cc. R. I.V.−H.	310	10.0	50	1.6
16	G-1313	6/ 5/34	7 yr.	20.0	13.3	15.8	31.6 51.7 67.8 71.5	5½ 7½ 11½ 30½	49.5	−17.9 + 2.2 +18.3 +22.0	567 575	7.93 6.27			51.7 64.2 49.1 41.6 28.9		56.3 32.4	857 614 536 399 234	480 cc. ⅙ M. I.V. 720 cc. ⅙ M. H.	200	10.0	40	2.5
17	K-1679	7/31/34	2 yr.	11.5	7.6	21.7	31.6 47.6	6½ 19½	55.7	−24.1 − 8.1	585 585	 			37.6			376 222 126	690 cc. ⅙ M. I.V.+H.	115	10.0	40	2.0
18	H- 319	10/25/34	13 yr.	40.0	26.7	12.2	24.4 33.5 45.4 54.9	2 3 5 8	45.8	−21.4 −12.3 − 0.4 + 9.1	479 521 550 560	9.96 8.40 8.05 7.85			45.4 71.8 63.0 42.8 25.2		49.0 44.0	1160 659 578 398 325 114	2400 cc. ⅙ M. I.V.+H.	400	10.0	40	2.0

*M. = Molar concentration.
I.V. = Intravenously.
I.P. = Intraperitoneally.

H. = Subcutaneously.
R. = Ringer's solution.
F.L.R. = Fortified Lactate-Ringer's solution.

D. = Died—No autopsy.
A. = Autopsy.
I. = Improved.

TABLE V — Continued

DATA INCIDENT TO RECOVERY FROM ACIDOSIS OF DIABETIC ORIGIN AFTER Na r-LACTATE THERAPY

				SERUM															THERAPY				
				Body		CO_2 Content—Vols. %					Nacl.	Protein	Alb.	Glob.	Lactic Acid	Inorg. P.	N.P.N.	Dextrose		Molar		Ringer's Solution	Insulin 1st 8 Hrs.
No.	Case	Date	Age	Wt. Kg.	H_2O Liter (Estimated)	Before	After	Hrs.	Expected	Difference	Mg. %	G.%	G.%	G.%	Mg. %	Mg. %	Mg. %	Mg. %	Na r-Lactate*	CC.	CC./Kg.	CC./Kg.	U./Kg.
19	L- 893	5/ 6/35	17 mo.	10.0	67.0	11.5	25.0 34.0 40.5 47.0 61.0	2½ 3½ 4½ 5½ 22½	45.0	−20.0 −11.0 − 4.5 + 2.0 +16.0					29.0 40.0 34.0 29.8 21.0 22.1			375 252 174 135 91 185	600 cc. ⅙ M. H.+I.P. +I.V.	100	10.0	40	2.0
20	I- 564	1/31/34	13 yr.	30.0	20.0	34.9	59.0	7	68.5	− 9.5								242 580 410	1800 cc. ⅙ M. I.V.+H.	300	10.0	—	1.0
21	H- 319	8/14/35	14 yr.	35.0	23.3	15.4	18.9 22.2 30.7 31.9 66.0	2½ 5 6½ 10½ 28	49.1	−30.2 −26.9 −18.4 −17.2 +16.9								727 520 228 135	2100 cc. ⅙ M. I.V.+H_2O	350	10.0	11	2.0
22	L-1807	9/ 1/35	4 yr.	15.0	10.0	13.1	14.6 24.9 36.1 38.6	2 4 6 17	46.7	−32.1 −21.8 −10.6 − 8.1								455 381 273 216 162	70 cc. M.+800 R. I.V. 80 cc. M.+550 R. I.P.	150	10.0	90	2.0
23	B-1826	9/27/35	14 yr.	40.0	26.7	14.5	40.8 40.5	5½ 24	48.1	− 7.3 − 7.6					47.8 57.9 44.1			502 155 375	400 cc.M.+2000 cc. H_2O I.V.+H	400	10.0	40	2.5
24	L-1850	9/6/35	8 yr.	18.8	12.5	9.1	51.0	9½	43.2	+ 7.8								478 55	190 cc. M.+950 cc. H_2O I.V.+H.	190	10.0	42	3.0
25	L-2244	10/31/35	5 yr.	15.0	10.0	11.1	50.6 62.1	6 16½	44.7	+ 5.9 +17.4		5.30 5.21 5.25	 2.77		23.0 30.0 27.7		22.2 17.0 13.5	503 87 41	 450 cc. ⅙ M. I.V. 450 cc. ⅙ M. H.	150	10.0	40	2.5
26	L- 893	7/20/36	3 yr.	12.0	8.0	26.0	57.6 65.5	5½ 13	59.7	− 2.1 − 2.1 + 5.8								215 72 75	720 cc. ⅙ M. I.V.−H.	120	10.0	—	0.4

27	J- 373	8/ 6/36	10 yr.	22.5	15.0	20.2 pH. 7.01	55.5 61.3 57.0	5¼ 22 25½	53.8	+ 1.7 + 7.5 + 3.2		5.35					18.0	372 90 375 77	220 cc.M.+ 1125 cc. H_2O I.V.+H.	220	10.0	39	2.0
28	H- 319	8/12/36	15 yr.	40.0	26.7	23.5	44.3	5½	57.1	−12.8								554 220	400 cc. M.+ 2000 cc. H_2O I.V.−H.	400	10.0	40	2.0
29	I- 429	8/20/36	13 yr.	40.4	26.9	19.5	50.3	5	53.6	− 3.3								562 74	410 cc. M.+2025 H_2O I.V.+H.	410	10.0	40	2.0
30	M-2099	11/ 6/36	10 yr.	23.0	15.3	15.0	50.2	4½	48.7	+ 1.5		7.97 7.43					30.0 26.0	330 167 336	230 cc. M.+1150 cc.H_2O I.V.−H.	230	10.0	40	2.0
31	I- 643	4/ 4/32	13 yr.	45.0	30.0	17.0	18.1 24.9 33.3 39.5 51.7 62.0 67.5	1½ 2 3 4 5 18½ 24	50.6	−32.5 −25.7 −17.3 −11.1 + 1.1 +11.4 +16.9	573	8.85			22.1 — 39.5 30.2 27.8 25.0 22.7 20.5	4.5	30.0	470 — 308 301 270 252 218 214 185	450 cc. M.+ 2400 cc. H_2O I.V.+H.	450	10.0	—	2.5
32	L- 855	4/29/35	11 mo.	8.0	5.3	9.6	14.5 16.0 17.5 20.5 24.5 47.9 65.0	2 3 4 5 6½ 11 23	39.3	−24.8 −23.3 −21.8 −18.8 −14.8 + 8.6 +25.7					22.0 12.6 6.0 12.6 6.0 10.0 13.0			553 378 275 215 163 105 180 149	70 cc. M.+ 350 cc. H_2O I.V.−H.	70	9.9	35	2.1
33	I-2441	12/20/32	6 yr.	17.7	11.8	15.1	25.7 35.2 51.2	2 4 20	47.3	−21.6 −12.1 + 3.9	579	8.99			30.2 39.4 23.4		31	500 287 89 60 56 50.5	170 cc. M.+ 900 cc. R. I.V.+H.	170	9.6	50	2.8
34	B- 218	8/21/36	13 yr.	46.3	30.9	13.5	54.2	5	43.9	+10.3								540 288	420 cc. M.+ 2100 cc. H_2O I.V.−H.	420	9.0	34	1.8
35	H-1054	5/ 1/31	12 yr.	30.0	20.0	16.1	35.2 52.0	4 22	44.1	− 8.9 + 7.9	603 556 538	8.58 7.33 8.76			64.3 51.5 42.3	3.9 2.0 3.0	27.0	508 278 40	250 cc. M.+ 600 cc. 5% glucose	250	8.3	—	3.0
36	H- 319	1/28/31	10 yr.	25.0	16.6	14.4	50.0	10½	41.4	+17.6	503 504	8.41 7.30				2.0	53.5 30.0	655 70	200 cc. M.+ 300 cc. R. I.V.	200	8.0	12	2.4
37	K- 372	2/11/34	10 yr.	18.6	12.4	25.2	52.8 62.5	10 24	51.9	+ 0.9 +10.6					18.9 28.9			240 154 87	500 cc. ⅙ M. I.V. 364 cc. ⅙ M. (H.)	148	7.7	27	1.6

*M. = Molar concentration.
I.V. = Intravenously.
I.P. = Intraperitoneally.

H. = Subcutaneously.
R. = Ringer's solution.
F.L.R. = Fortified Lactate-Ringer's solution.

D. = Died—No autopsy.
A. = Autopsy.
I. = Improved.

TABLE V — Continued

DATA INCIDENT TO RECOVERY FROM ACIDOSIS OF DIABETIC ORIGIN AFTER Na r-LACTATE THERAPY

				SERUM															THERAPY				
				Body		CO_2 Content—Vols. %					Nacl.	Protein	Alb.	Glob.	Lactic Acid	Inorg. P.	N.P.N.	Dextrose		Molar		Ringer's Solution	Insulin 1st 8 Hrs
No.	Case	Date	Age	Wt. Kg.	H_2O Liter (Estimated)	Before	After	Hrs.	Expected	Difference	Mg. %	G.%	G.%	G.%	Mg. %	Mg. %	Mg. %	Mg. %	Na r-Lactate*	CC.	CC./Kg.	CC./Kg.	U./Kg.
38	I-1977	10/ 6/32	10 yr.	25.0	18.6	33.8	64.0	11	68.8	− 4.8								293 144	635 cc. ⅙ M. I.V. 460 cc. ⅙ M. (H.)	182	7.3	—	0.8
39	H- 319	6/14/34	13 yr.	36.0	24.0	32.0	50.7	5½	56.3	− 5.6								489 166	260 cc. M.+ 1300 cc. R. I.V.+H.	260	7.2	44	1.2
40	I- 564	3/21/32	11 yr.	20.0	13.3	35.0	66.0 65.4	8 16	58.6	+ 7.4 + 6.8		7.50	3.38	4.12			40.0	475 63 365 60	140 cc. M.+ 800 cc. H_2O H.	140	7.0	—	1.5
41	I-1479	7/28/32	4½ yr.	14.4	9.6	16.2	35.8 47.2	2 18½	39.6	− 3.8 + 7.6	608	6.96			23.9 32.8		37.0	437 150 243	200 cc. ⅙ M., I.V. 400 cc. ⅙ M. (H.)	100	6.9	—	2.5
42	I-429	2/29/32	9 yr.	21.9	14.6	13.6	18.8 22.4 23.5 31.8 54.2	2 3 4 5 19	36.6	−17.8 −14.2 −13.1 − 4.8 +17.6	544	7.60			32.0 63.0 35.0 33.2 29.6	4.2	33.0	543 427 357 300 300 172	150 cc. M.+ 900 cc. R., I.V. H.	150	6.8	82	3.9
43	H-1054	8/21/31	12 yr.	33.0	22.0	15.0	42.0	5½	36.4	+ 5.6								316 135	210 cc. M.+440 cc. R., I.V. H.	210	6.4	32	1.2
44	L-2044	10/ 3/35	7 yr.	22.9	15.3	33.8	63.8 65.7	16 19	52.1	+11.7 +13.6								359 41 42 151 424	125 cc. M.+ 625 cc. H_2O, I.V. H.	125	5.4	35	0.4
45	D-1748	12/25/30	6 yr.	23.0	15.3	34.0	59.6	6	52.5	+ 7.1									120 cc. M.+125 cc. R. I.V.	120	5.4	5	0.9
46	G-2520	5/22/33	14 yr.	54.0	36.0	31.3	57.2 58.9	4 20	46.8	+10.4 +12.1								40 56 383	250 cc. M.+ 800 cc. H_2O I.V.+H.	250	4.6	—	0.18

48	C-1636	2/ 7/32	17 yr.	56.8	37.9	29.0	61.5 70	13	36.7	+24.8								135 70	130 cc. M.+ 400 cc. H_2O I.V.+H.	130	2.3	8	1.0
49	D-1913	3/ 9/31	15 yr.	50.0	33.3	27.5	56.0 66	16½	34.2	+21.8								678 66	100 cc. M.+300 cc. R. I.V.	100	2.0	14	1.8
50	L- 893	1/25/37	3½ yr.	15.2	10.1	23.0	51.0 54.4	4 11	56.0	− 5.0 − 1.6								223 201 189	152 cc. M.+ 760 cc. H_2O I.V.−H.	152	10.0	40	0.73
51	N- 410	3/ 5/37	2 yr.	9.1	6.0	18.0	39.0 40.0 49.5	7 11 20	51.7	−12.7 −11.7 − 2.2								456 860 40 52	182 ⅙ M. I.V. 364 ⅙ M. H.	91	10.0	40	2.0
52	D- 689	3/ 7/37	12 yr.	31.1	20.7	19.0	44.0 46.0 63.0	6½ 13½ 21½	52.6	− 8.6 − 6.6 +10.4								452 199 50 186	310 cc. M.+ 1550 cc. H_2O I.V.+H.		10.0	40	1.4
53	N-1252	7/19/37	23 mo.	9.0	6.0	9.0	29.2 36.6 46.1 59.8	2 4 6 26½	42.6	−13.4 − 6.0 + 3.5 +17.2								532 234 187 163 126	90 cc. M.+ 450 cc. H_2O, I.V.+H.	90	10.0	40	2.0
54	L-2531	9/ 5/37	8 yr.	25.0	16.6	9.9 pH. 7.24	17.1 17.3 22.4	2 3 5	43.6	−26.5 −26.3 −21.2		6.34			26.8 52.7 26.2		26.0	334 308 180	250 cc. M.+ 1250[12] H_2O I.V.+H.	250	10.0	40	2.0
55	L-2531	9/ 5/37	8 yr.	25.0	16.6	22.4 pH. 7.33	53.7 52.0	5½ 10½	56.1	− 2.4 − 4.1					20.6			122 20.4	250 cc. M.+ 1250 cc. H_2O I.V.+H.	250	10.0	40	0.8
56	L-1850	10/ 5/37	10 yr.	23.2	15.5	9.5 pH. 7.08	 40.2 45.3 62.0	 6¾ 11½ 18½	43.3	 − 3.1 + 2.0 +18.7		6.74 5.50			29.1 42.0 36.8		27.0 20.0	345 64.4 58 62	232 cc. M.+ 1150 cc. H_2O ½ I.V. ½ H.	232	10.0	40	2.0
57	N-2070	11/11/37	12 yr.	40.0	26.2	29.3 pH. 7.30	 62.5 76.0	 6½ 16	62.9	 − 0.4 +13.1		7.41 6.57			24.0 29.0 16.4		27.0 17.5	355 120 108	400 cc. M.+ 2000 cc. H_2O I.V. H.	400	10.0	40	2.0

*M. = Molar concentration.
I.V. = Intravenously.
I.P. = Intraperitoneally.

H. = Subcutaneously.
R. = Ringer's solution.
F.L.R. = Fortified Lactate-Ringer's solution.

D. = Died—No autopsy.
A. = Autopsy.
I. = Improved.

It is of interest to compare the observed rises in carbon dioxide content with those calculated at different times after the commencement of treatment:

3 Hours After Beginning Treatment (53 Cases)

Less than expected (−)				More than expected (+)
>30 vol. %	30-20 vol. %	20-10 vol. %	10-0 vol. %	0-10 vol. %
(2) = 3.8%	(19) = 35.8%	(21) = 39.6%	(10) = 18.9%	(1) = 1.9%

Average = 17.4 vol. %

6 Hours After Beginning Treatment (48 Cases)

Less than expected (−)				More than expected (+)	
>30 vol. %	30-20 vol. %	20-10 vol. %	10-0 vol. %	0-10 vol. %	10 vol. %
(1) = 2.3%	(5) = 11.3%	(11) = 25.0%	(19) = 43.2%	(7) = 15.8%	(1) = 2.3%

Average = 8.1 vol. %

12 Hours After Beginning Treatment (34 Cases)

Less than expected (−)			More than expected (+)		
30-20 vol. %	20-10 vol. %	10-0 vol. %	0-10 vol. %	10-20 vol. %	20-30 vol. %
(1) = 2.9%	(3) = 8.8%	(10) = 29.4%	(12) = 35.2%	(7) = 20.6%	(1) = 2.9%

Average = +1.2 vol. %

18 Hours After Beginning Treatment (23 Cases)

Less than expected (−)		More than expected (+)		
20-10 vol. %	10-0 vol. %	0-10 vol. %	10-20 vol. %	20-30 vol. %
(2) = 8.7%	(5) = 21.7%	(8) = 34.8%	(7) = 30.4%	(1) = 4.3%

Average = +4.0 vol. %

24 Hours After Beginning Treatment (8 Cases)

Less than expected (−)	More than expected (+)	
10-0 vol. %	0-10 vol. %	10-20 vol. %
(2) = 25.0%	(3) = 37.5%	(3) = 37.5%

Average = +5.9 vol. %

V. ACIDOSIS OF SEVERE INFECTIONS AND MISCELLANEOUS CAUSES

Here also pathogenesis may be complex, and contributory factors frequently are ketosis, circulatory or renal failure, either of which may be organic or functional, and loss of gastrointestinal secretions by vomiting, diarrhea or fistula, and acid administration. We have 26 examples of acidosis of this type, 20 being relieved satisfactorily (Table VI). Of the 6 exceptions, one (Case 7) is to be explained by the inadequate dose of

sodium lactate, 5.8 c.c. molar per kilogram body weight; in cases 12, 19, and 22, second therapeutic injections of lactate proved effectual. The following data compare the observed values following institution of treatment with those expected:

Less than expected (−)				More than expected (+)
30 vol. %	30-20 vol. %	20-10 vol. %	10-0 vol. %	0-10 vol. %
(3) = 12.0%	(7) = 28.0%	(7) = 28.0%	(4) = 16.0%	(4) = 16.0%

Average = −15.4%

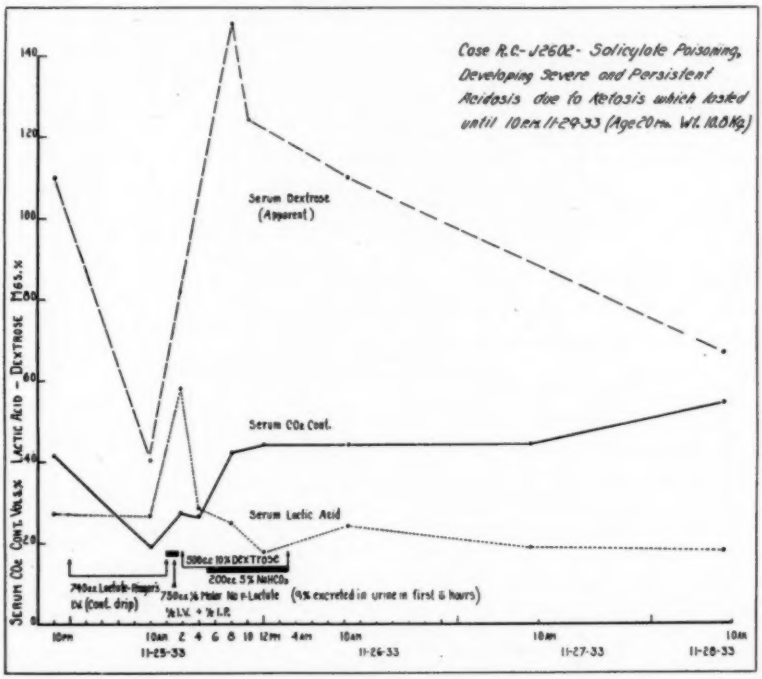
Case R.C.-J2602- Salicylate Poisoning, Developing Severe and Persistent Acidosis due to Ketosis which lasted until 10 a.m. 11-29-33 (Age 20 mo. Wt. 10.0 Kg.)
Serum Dextrose (Apparent)
Serum CO2 Cont.
Serum Lactic Acid
500cc 10% DEXTROSE
200cc 5% NaHCO3
(9% excreted in urine in first 6 hours)
Serum CO2 Cont. Vols.% Lactic Acid - Dextrose Mgs.%
10pm
10am 11-25-33
2 4 6 8 10 12m 4am
10am 11-26-33
10am 11-27-33
10am 11-28-33

Chart 4.—Case of salicylate poisoning with severe ketosis and acidosis treated successfully with sodium r-lactate, dextrose, and sodium bicarbonate.

The underlying infections in this group included various types of severe upper respiratory tract infections with blood stream involvement, meningitis, septic thrombophlebitis, and suppurative nephritis. It should also be mentioned that many of these patients were moribund at the time of treatment of the acidosis.

The case of salicylate poisoning (Cases 12 and 13, Table VI, and Chart 4) is of special interest:

This infant aged 20 months was brought to the hospital one night with the history that following the ingestion of 14-16 tablets, later found to be

TABLE

RECOVERY FROM ACIDOSIS OF SEVERE INFECTIONS AND

No.	Case	Date	Age	Body			Serum*												
							Vols. %		CO_2 Content			NaCl	Gm. % Protein			Lactic Acid	Inorg. P.	Ca.	N.P.N.
				Wt. Kg.	Water Liters	Edema	Before	After	Hrs.	Expected	Difference	Mg. %	Total	Alb.	Glob.	Mg. %	Mg. %	Mg. %	Mg. %
1	G-2127	12/14/30	5 wk.	4.7	3.1		23.5	42.5	4	54.2	−11.7								
2	G- 814	8/ 5/30	2 yr.	9.4	6.2		29.5	49.8	5	58.4	− 8.6	632							
3	H- 778	4/ 3/31	3 wk.	2.8	1.8		12.4	28.8	20	49.7	−20.9	747				40.1			
4	H- 992	4/24/31	2 wk.	3.6	2.4		19.8	36.2	2	75.8	−39.6	684 585							
5	H-1047	5/22/31	6 wk.	3.2	2.1		16.4	45.0	13½	88.4	−43.4	747				40.0			
6	H- 978	5/ 9/31	4 da.	2.6	1.7		25.0	56.9	3	75.5	−18.6								
7	H-2457	10/28/31	3 mo.	3.6	2.4		28.0	32.0	18	47.6	−15.6	813 784				56.7 26.5			105.0 77.0
8	H-2457	10/28/31	3 mo.	3.6	2.4		28.3	54.0	12	60.9	− 6.9	796 702	7.45 7.20			21.0 15.0			56.0 67.0
9	I-1193	6/19/32	1 yr.	8.0	5.3		16.7	46.0	15	41.0	+ 5.0								
10	I-2159	10/31/32	21 mo.	7.8	5.2		26.7	40.6	12	45.2	+ 4.6	632	5.20				4.5		90.0 79.0
11	I-2017	10/12/32	5 yr.	12.0	8.0		18.7	44.2	16	52.3	− 8.1								
12	J-2602	11/24/33	20 mo.	10.8	7.2		18.8	26.2	4	57.8	−31.6								
13	J-2602	11/25/33	20 mo.	10.8	7.2		26.2	42.2	3	62.5	−20.6								
14	J-3499	12/ 6/33	5 mo.	4.7	3.1		23.9	51.9	6	59.9	− 0.8	668	4.95				9.0		198.0
15	K-2038	9/12/34	4 mo.	5.0	3.3		14.3	35.9	8	51.4	−11.7		7.28			32.0	5.8		34.0
16	K-2038	9/30/34	4 mo.	4.4	2.9		18.3	41.9	23	41.4	+ 0.5	608							21.0
17	K-2789	12/31/34	19 mo.	6.7	4.5		18.7	31.0	5	51.0	−20.0								
18	L-2633	1/ 1/36	19 mo.	12.0	8.0		20.1	43.5	17	53.6	−10.1								
19	M -246	1/26/36	15 da.	2.4	1.6		16.5	30.5	25	54.3	−23.9								50.0
20	M- 246	1/27/36	16 da.	2.6	1.7		30.5	52.0	26	62.1	−10.1	661 683	5.30			66.5 65.4			32.0
21	—	10/ 8/37	24 yr.	50.0	33.3		15.5	38.4	16½	49.2	−10.8								
22	N-1993	10/31/37	2 wk.	2.2	1.4		14.3	19.5	5	49.4	−29.9						9.2		91.3
23	N-1993	10/31/37	2 wk.	2.2	1.4		19.5	22.1	12	51.5	−29.4	655							80.5
24	N-1993	10/31/37	2 wk.	2.2	1.4		22.1	55.3	17½	77.5	−22.2								80.5
25	N-2072	11/11/37	11 mo.	6.5	4.3		10.7	17.8	6	44.2	−26.4					35.5			51.8
26	N-2072	11/12/37	11 mo.	6.5	4.3		17.8	35.0	15	52.2	−17.2								

*When double figures are given, the lower denote determinations after treatment.
†M. = Molar concentration.
I.V. = Intravenously.
I.P. = Intraperitoneally.
H. = Subcutaneously.
R. = Ringer's solution.
L.R. = Lactate-Ringer's solution.
F.L.R. = Fortified Lactate-Ringer's solution.
D. = Died — No autopsy.
A. = Autopsy.
I. = Improved.

sodium salicylate, he developed a convulsion and began to vomit. Because of the presence of mild acidosis and persistent vomiting even after gastric lavage, it was decided to give him lactate-Ringer's solution throughout

VI

MISCELLANEOUS CAUSES AFTER SODIUM r-LACTATE THERAPY

Na r-Lactate†			Ringer's	Dextrose		Diagnosis — Remarks	Outcome
	Molar						
	cc.	cc./kg.	cc./kg.	cc.	%		
45 cc. M. I.V.	45.0	9.5		170	10	Acute mastoiditis—streptococcus hemolyticus; diarrhea.	D. 2/15/30
80 cc. M.+120 H_2O	80.0	8.5				Mastoiditis.	I.
30 cc. M.+60 cc. H_2O I.V.	30.0	10.7	14.0			Extensive thrombophlebitis; gangrene, septicemia, circulatory failure.	A. 4/ 7/31
60 cc. M.+400 cc. H_2O H.	60.0	16.6				Otitis media, pneumonia, diarrhea, incomplete fluid absorption.	D. 4/26/31
67.5 cc. M.+H_2O I.V.+H.	67.5	21.0		200	5	Mastoiditis, hemolytic streptococcus, circulatory failure.	D. 5/23/31
240 cc. ⅙ M. I.V.	40.0	15.4				Spina bifida, neurogenic bladder, cystotomy, anuria.	D. 5/ 9/31
21 cc. M.+50cc.—5% Dext. I.V.	21.0	5.8	19.0	50	10	Thrombophlebitis of lateral sinus, athrepsia, vomiting, diarrhea.	A. 11/ 1/31
20 cc. M.+100 cc. Dextrose 15 cc. M.+75 cc. Dextrose I.V.	35.0	9.7		975	10		
H.	60.0	2.5	37.5	240	5	Starvation ketosis following attempt at weaning.	I.
43 cc. M.+165 cc. Dextrose I.V.	43.0	5.5	51.0			Otitis media, laryngitis, pneumonia, athrepsia, anemia.	A. 11/ 5/32
120 cc. M.+800 cc. H_2O I.V.+H.	120.0	10.0				Scarlet fever, mastoiditis, thrombophlebitis of lateral sinus.	A. 12/17/32
	135.0	11.6				Salicylate poisoning, ketosis, see Chart 4.	I.
50 cc. M. I.V.	50.0	10.6				Otitis media, erysipelas, thrombophlebitis, pyonephritis with infarcts, septicemia—strep. hemo.	A. 12/ 6/33
150 cc. ⅙ M. I.V. 150 cc. ⅙ M. I.P.	50.0	10.0	40.0			Acute suppurative nephritis—B. coli.	D. 10/11/34
185 cc. ⅙ M. I.V.+H.	31.0	7.0					
⅙ M. I.V.+H.	65.0	9.7	39.0			Pneumonia, jaundice, circulatory failure. Fluids incompletely absorbed.	D. 12/31/34
⅙ M. I.V.+H.	120.0	10.0	33.0			Acute laryngotracheal bronchitis—strep. hemo.	I.
⅙ M. I.V.+H.	27.0	11.2	52.0			Prematurity, diarrhea, jaundice, fatty infiltration of liver, cardiac dilatation, circulatory collapse.	A. 3/24/36
⅙ M. I.V.+H.	24.0	9.2	38.0				
⅙ M. I.V.+H.	500.0	10.0	40.0			Diethylene glycol poisoning, adult.	D. 10/12/37
200 cc. ⅙ M. I.V.+H. 200 cc. R. H.	22.0	10.0	40.0			Thrombi in veins of kidney, adrenal, brain and spleen with early infarcts of brain and kidney, broncho-pneumonia, septicemia—B. coli.	A. 10/ 8/37
200 cc. F.L.R. H.	20.0	10.0	80.0				
220 cc. F.L.R. I.V.+H. 200 cc. L.R. H.	40.0	15.3	11.0				
390 cc. ⅙ M. I.V.+H.	65.0	10.0	40.0			High fever of undetermined origin, vomiting, starvation, dehydration.	I.
390 cc. ⅙ M. I.V.+H.	65.0	10.0	40.0				

the night by the continuous intravenous drip method. Much to our surprise the next morning we noted signs of severe acidosis and stupor. Despite the administration of 740 c.c. of lactate-Ringer's solution during the night, the serum carbon dioxide content had dropped from 42.0 to

18.8 volumes per cent. During the same interval the "apparent" blood sugar had dropped from 110 to 40 (26 "true") mg. per cent, and acetone could be detected on the breath and in the urine. Strongly positive tests for both aceto-acetic acid and salicylate in the urine were also obtained. Seven hundred and fifty cubic centimeters of one-sixth molar sodium *r*-lactate were then given, half intravenously and half intraperitoneally, and much to our uneasiness, the serum carbon dioxide content rose only to 26.2 volumes per cent (expected 57.8). At this time we wondered whether with the enlarging liver and the severe ketosis the metabolism of lactate might have been interfered with, and consequently decided to add sodium bicarbonate to the 10 per cent dextrose which was being given by the continuous drip method, because of the hypoglycemia and ketosis. When 200 c.c. of 5 per cent sodium bicarbonate had been given, the serum carbon dioxide content had risen only to 42.2 volumes per cent (expected 62.5). Later when lactic acid was determined in the blood and urine, and the duration and extent of ketosis followed, the explanation of the apparent partial failure of both sodium *r*-lactate and sodium bicarbonate to relieve completely the acidosis became clear (Chart 4): Lactate was metabolized normally but the amount of sodium released as well as the amount of sodium administered as the bicarbonate salt was quantitatively insufficient to balance completely the base binding effect of the ketone acids, which continued to be formed in large amounts for about five days. Undoubtedly larger amounts of sodium *r*-lactate were indicated both for its anti-acidotic and glycogenic effects.

COMMENT

In considering the efficiency of sodium lactate therapy for different types of acidosis from the quantitative viewpoint, we note that in the group of diabetics, after twelve hours values expected from our method of calculation were almost exactly realized, but "undershooting" tended to occur in the other groups. Such "undershooting" was minimal and generally negligible for the group with renal insufficiency, but was considerable and frequently of some consequence in the groups with diarrhea and severe infections. Before attempting to explain such discrepancies as did occur, we should first point out that our method of calculating expected values of bicarbonate concentration is at the best only a very rough one. In the first place, the amount of sodium lactate excreted into the urine is not considered. Such a loss is appreciable in normal individuals in whom diuresis with the excretion of highly alkaline urine follows promptly the intravenous injection. The situation is quite different, however, in subjects with severe acidosis, particularly when dehydration is also present. In such individuals diuresis, if it occurs to any extent at all, is usually not attended by the excretion of significant amounts of lactate because the delay in its appearance is usually long enough to permit the level of blood lactate to fall to ap-

TABLE VII

DATA ON URINARY EXCRETION OF LACTATE IN CASES OF DIABETIC ACIDOSIS

SUBJECT	MOLAR SODIUM *r*-LACTATE GIVEN				EXCRETED	
	C.C. TOTAL	C.C./KG.	ROUTE	TIME (MIN.)	PER CENT	(HR.)
P. K.	150	7.0	I.V.	(60)	6.5	(6)
D. B.	310	10.0	I.V.-I.P.-H.		9.3	(11)
W. T.	150	10.0	I.V.-I.P.-H.		8.8	(13)
D. B.	400	11.5	I.V.-H.		15.2	(9)

proximately normal values (Table VII). Furthermore, in subjects with severe acidosis, the urine is not immediately rendered alkaline by the injection of the usual therapeutic dose of sodium lactate, and it is probable that for that reason there is even relatively less loss of sodium than lactate. It would seem, therefore, that no serious discrepancy in the calculation of the theoretical rise of bicarbonate should result from failure to consider the amount of injected lactate escaping into the urine. Failure to consider, however, the base-claiming effect of buffer substances other than bicarbonate would seem to be a much more important omission. During the development of acidosis, should the pH of the blood and body fluids fall from 7.4 to 7.0 (which frequently happens), we should expect from the work of Van Slyke, Hastings, and Neill[9] that about 10 milliequivalents of alkali per liter of blood would be yielded by buffers other than bicarbonate, when the latter would be yielding approximately 18 milliequivalents, and similarly would be claimed by such buffers during the recovery process. Tissue buffers would be expected to behave similarly, and the net result should be a dissipating effect by such buffers on the conversion of sodium lactate into sodium bicarbonate when severe acidosis is completely relieved. By such a mechanism itself it is conceivable that as much as 35 per cent of a "therapeutic" dose of lactate may fail to be converted into bicarbonate. In the extremely dehydrated individuals, furthermore, the injection of fluid is usually followed by permanent water retention which goes to re-establish a normal body water content. Such a gain in the volume of body water, if the dosage of lactate were based on the original weight, would further widen the difference between expected and actual rises of bicarbonate. These two last mentioned factors seem to account for the poor agreement between actual and calculated bicarbonate concentrations noted in the subjects with severe acidosis associated with diarrhea, dehydration, and severe infections (Tables IV and VI). Furthermore, such discrepancies should be magnified if the dosage of sodium lactate were enough to have resulted in alkalosis of the base bicarbonate excess type, for in such a case a restraining effect on the rise of base bicarbonate would result from its rapid compensatory excretion into the urine.

While such factors as the above mentioned would tend to lead to a lower bicarbonate concentration than that expected by our method of

calculation, at times there might be at least two operating in the opposite direction. In subjects in whom ketosis contributed to the acidosis, antiketogenic measures operating simultaneously with the liberation of sodium from combination with lactate would certainly tend to favor bicarbonate restoration, and so also would any renal activity concerned with the excretion of acid in an unneutralized state, or bound to ammonia.

With such modifying factors in mind, we may now consider and compare results actually obtained with those calculated. In the group of cases with renal insufficiency (Table III), ketosis is either nonexistent or is negligible; dehydration, while occasionally present and severe, is usually absent—in fact, edema is not uncommonly present; there can be little excretion of ammonia bound to acid, and there is also a reduced ability to excrete urine of high acidity. We would, therefore, expect good agreement between calculated and realized increases of bicarbonate except in the cases with very low blood hydrogen ion concentration and except in those with significant dehydration. Such seems to be the case (Table I). In the group with diarrhea, except when the latter was due to infection with the dysentery bacillus, modifying factors would tend to restrict bicarbonate increase and in this group we frequently see substantial discrepancies between expected and realized values. On the other hand, in the group with diabetes, ketosis is usually of a degree sufficient to balance or even slightly overbalance dissipating factors, and good agreement usually existed after twelve hours between calculated and realized bicarbonate concentrations (Table V). The poorest agreement is to be found in the group with severe infections (Table VI). Many of these patients were moribund at the time of treatment, and in addition to the possibility of operation of some or all of the "dissipating" factors mentioned above would also be circulatory failure leading to retarded absorption of fluid injected subcutaneously, tissue anoxia, and liver damage, all conceivably leading to some delay in the metabolism of lactate.

Actual failure to restore within twelve hours even very low bicarbonate values to 35-70 volumes per cent occurred in only 8 cases out of a total of 273 treated. These apparent failures are shown in Table VIII. In 4 instances, it should be noted, however, that after a second dose of sodium lactate had been given, satisfactory relief occurred. The explanation almost certainly is that with the development of very severe acidosis which permits the pH of the blood and body fluids to fall to the neighborhood of 7.0, buffer substances yield base to support the falling bicarbonate, claiming base again as it is released from metabolism of sodium lactate during the recovery process, and in that way dissipate the effect of the conversion of sodium lactate into sodium bicarbonate. Taking this into consideration, together with the fact that in general the most severe degrees of acidosis are to be found associated with dehydration of diarrheal origin in young infants, especially in the presence of

TABLE VIII

CASES OF ACIDOSIS FAILING TO RECOVER PROMPTLY AFTER SODIUM *r*-LACTATE THERAPY

CAUSE OF ACIDOSIS	HIST. #	AGE	SERUM CO_2 CONTENT VOLS. PER CENT				MOLAR NA LACTATE C.C. KG.	PROBABLE EXPLANATION
			BEFORE	AFTER (HRS.)	EXPECTED	DIFFERENCE		
Starvation and dehydration (premature)	M-246	15 da.	16.5 30.5	30.5(25) 52.0(26)	54.3 62.1	−23.9 −10.1	10.0	
Diabetes	L-2531	6 yr.	9.7 19.1	19.1(5) 52.8(4½)	55.0 64.4	−35.9 −11.6	11.0 11.0	Fixed base depletion?
Infection and renal insufficiency	L-2359	18 da.	22.0 30.0	30.0(19) 70.0(34)	61.6 69.6	−31.6 + 0.8	12.0 12.0	Second dose of lactate in each instance gave better response than first.
Renal insufficiency	N-487	5 mo.	9.0 25.0	25.0(6) 50.0(16)	41.0 57.0	−16.0 − 7.0	9.5 9.5	
Salicylate poisoning (ketosis)	J-2602	20 mo.	18.8 26.2	26.2(4) 42.2(3)	57.8 62.5	−31.6 −20.3	11.6 11.0 ($NaHCO_3$)	Continued acid formation.
Diarrhea (premature)	L-1554	14 da.	12.9	30.1(13)	42.7	−12.6	9.0	Moribund; died 15 hours later.
Ac. Bacillary dysentery	M-1411	5 mo.	12.0	16.0(11)	55.0	−39.0	12.8	Died 17 hours later.
Diarrhea and infection	H-778	21 da.	12.4	28.8(20)	49.7	−20.9	10.7	Base depletion (?) plus circulatory failure.

serious infection, and because in comparing expected rises of blood bicarbonate with those actually occurring in such cases of acidosis, an appreciable "undershooting" was noted in approximately half of the cases and no appreciable "overshooting" occurred, it has been our policy for some time to make 15 c.c. of molar sodium *r*-lactate per kilogram our routine dose in such cases (i.e., 90 c.c. of isotonic or ⅙ molar per kilogram) instead of 10 c.c. which we had first recommended and which still seems best for cases of acidosis of renal or diabetic origin. With the 50 per cent increase in dosage, initially very low carbon dioxide contents are much more consistently being brought to normal with the single initial administration of sodium lactate. In one instance, the case of salicylate poisoning, it should be noted that an unusual form of acidosis was present

in that acid was being generated at an unusually rapid rate, and that repeated administration of alkali was necessary. In 2 cases (L-1554 and M-1411), however, the failure cannot be explained on any such ground and seems due to the fact that the infants were moribund at the time, and perhaps for that reason lactate metabolism was ineffectual. In such infants failure to respond properly to sodium lactate therapy might be due, as suggested by Minot, Dodd, and Saunders,[10] to liver damage and derangement of lactic acid metabolism secondary to guanidine intoxication. If such were the case, however, one would expect initially high blood lactic acid levels to increase and remain even higher after injections of sodium lactate, which we have not observed. Perhaps such cases could be better treated with at least an initial dose of sodium bicarbonate.

SUMMARY AND CONCLUSIONS

1. Following the intravenous injection of sodium lactate the urinary excretion of lactic acid was considerably greater when the "racemic" mixture was given than when a corresponding amount of the *l*+ isomer was administered. This observation suggests that the *l*+ isomer is utilized more readily than the *d*– form.

2. The increases in oxygen consumption during and after intravenous injection of both "racemic" and sodium *l*+ lactate were quite variable but were not enough larger on the whole than the increases with the injection of an equivalent amount of sodium bicarbonate to account for the disappearance of the lactic acid on the basis of an oxidation quotient of 4 for *l*+lactate and of one for the *d*– isomer. It seems quite probable, therefore, that part of both the *l*+ and *d*– isomers which disappeared replaced other food stuffs in metabolism.

3. By means of the intravenous injection of sodium *r*-lactate the acidosis of renal origin was satisfactorily relieved; that is, the observed carbon dioxide content was raised within twelve hours to a normal value or to one in the zone of just mild acidosis (35-45 volumes per cent) in 11 patients on whom follow-up data were obtained in 15 out of 16 instances. In the single exception a second injection was necessary. In many more cases, without follow-up data, apparently satisfactory relief was obtained. In the chronic type of renal insufficiency when vomiting is absent or negligible, the continued oral administration of sodium lactate may be effective in relieving acidosis and in preventing its recurrence.

4. Sixty cases of acidosis associated with nonspecific diarrhea and 8 associated with acute bacillary dysentery were treated with sodium lactate, and follow-up data indicated that all but three of these were satisfactorily relieved. One hundred more cases with acidosis associated with nonspecific diarrhea and 41 with acute bacillary dysentery were treated with apparent success, but without follow-up data.

5. Fifty-five cases of diabetic acidosis were treated with sodium lactate, only 2 being unsatisfactory by definition, and in only one case did the carbon dioxide content rise to more than 80 volumes per cent. Two deaths occurred in the group, a mortality of 3.6 per cent.

6. In a group of 26 patients with acidosis of severe infections and miscellaneous causes, 20 were relieved satisfactorily of their acidosis. In one of the unsatisfactory cases, less than the usual dose of lactate was given, and in 3 others, a second injection proved effectual.

7. Actual failure to restore within twelve hours even very low bicarbonate values to 35 to 70 volumes per cent occurred in only 8 out of a total of 273 cases. The reasons for these apparent failures are discussed. It is suggested that in cases of very severe acidosis with the serum pH value probably approaching 7.0, 15 c.c. of molar sodium lactate per kilogram be given (i.e., 90 c.c. of isotonic or one-sixth molar per kilogram) instead of 10 c.c. which was first recommended and which still seems best for acidosis of renal or diabetic origin.

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500 SOUTH KINGSHIGHWAY

ACUTE EPIDEMIC ENCEPHALITIS IN ST. LOUIS

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FOREWORD

THE epidemic of acute encephalitis which occurred in St. Louis in 1933 called attention to a serious infectious disease the presence of which had not been previously recognized in the western hemisphere. In a volume such as this, dedicated to the late Dr. W. McKim Marriott, it is interesting to note that Marriott himself was one of the first sufferers from the disease, the diagnosis being further complicated by the fact that he had left the city when the initial symptoms arose. Fortunately, after a stormy illness, his recovery was complete.

* * *

In the last five years St. Louis and its suburbs has been visited by two severe epidemics of encephalitis. The first of these occurred in the summer of 1933 and the next in the summer of 1937. In the earlier epidemic over 1,100 cases of the disease were reported, with a mortality rate of about 20 per cent (22.5 per cent in the city proper), whereas in 1937 only 431 cases were reported with 107 deaths (24.8 per cent mortality). The two epidemics ran a parallel course so far as seasonal incidence and symptomatology were concerned, but the 1937 cases showed a slightly higher mortality rate, and children were somewhat oftener affected than was the case in 1933. In contrast to most infectious diseases, both incidence and mortality rate increased with advancing age, the latter being markedly affected by the presence of other pathologic processes such as cardiorenal disease, which might be present. It is interesting to note that Japan has had at least thirteen epidemics of a clinically similar disease, in one of which, in 1924, the number of cases reached almost 7,000 with a mortality rate of nearly 60 per cent.

ETIOLOGY

Early in the 1933 epidemic Muckenfuss, Armstrong, and McCordock, and later Webster and Fite succeeded in isolating a filtrable virus which, when injected intracerebrally into monkeys and mice, or instilled into the nostrils of the latter, produced the disease. Serum from patients recovering from the disease shows neutralizing properties for the virus, whereas that obtained from individuals who have had the so-called lethargic (von Economo) encephalitis fails to neutralize. Up to the present time, nine strains of the virus have been isolated in the laboratories of Washington University School of Medicine and the viruses

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recovered in 1933 and 1937 have been shown to be immunologically identical. The mode of transmission appears to be through contact infection rather than by way of food, water, or insects. Multiple cases in one family occurred but were very unusual.

INCUBATION PERIOD

By direct intracerebral inoculation this was usually eight to fourteen days in monkeys and five days in mice. Although not definitely established in human beings, the incubation period is probably between eight and fourteen days.

PATHOLOGY

The characteristic lesions are in the central nervous system and consist of intense congestion with petechial hemorrhages, cellular infiltration, and degenerative changes in the nerve cells. There occurs a cufflike infiltration of round cells about the blood vessels and small focal collections of cells elsewhere in the cortex, midbrain, medulla, pons, and upper levels of the cord. In contrast to the picture in lethargic encephalitis, except in the severest cases, the basal nuclei often escaped involvement.

SYMPTOMS

The symptoms commonly observed are in part those frequently found in many infectious diseases, plus another group indicative of involvement of the central nervous system. Briefly, the onset is usually abrupt with high fever and pronounced meningeal symptoms, but the latter were often masked by muscular aches, vomiting and abdominal pains, or other signs of a general infection. Despite the serious and often alarming picture presented by the patient in the early stages of the illness, recovery was ordinarily rapid and sequelae of an objective nature rare. For purposes of description it is convenient to discuss the clinical course of the disease by dividing the cases into three different groups although frequently one type of the disease merged indistinguishably into another.

Type I.—The most frequent clinical course of the disease was that in which the encephalitic symptoms dominated the picture from the very beginning. The onset was usually sudden, ushered in by malaise and perhaps chilly sensations, or occasionally convulsions, to be followed in rapid succession by headache, vomiting, and high fever (103° to 105° F.—39.4° to 40.6° C.). Such patients as were sufficiently rational frequently complained of muscular pains, abdominal cramps, and, in some instances, of sore throat and photophobia. Stiffness of the neck and even of the lower spine was frequent but may be absent even in cases of considerable severity. At the same time, in all but the mildest cases, some degree of mental confusion, sluggishness, or increasing drowsiness was present, although rarely was the coma so deep that the

patient could not be aroused momentarily at least. At times mild delirium and insomnia or hyperexcitation replaced apathy and somnolence. Moreover, many patients were disoriented as to time and place and had no recollection of events during the early stages of the illness. Tremors, involving especially the hands, tongue, and lips, were common, and speech was thick, slurred, and often unintelligible. Less frequently, however, complete aphasia occurred. In a few cases, too, there was a marked cerebellar type of ataxia present, which had usually disappeared by the end of the second week.

The neurologic examination further revealed that the Kernig sign was frequently positive but not always in proportion to the amount of neck rigidity present. Absence of the abdominal reflexes was the rule in adults, but in children these were often normally present throughout the entire illness. The knee jerks were irregular, being normal at some times and perhaps absent or exaggerated at others, even in the same cases. Similarly, plantar reflexes might be normal at one examination and abnormal a few hours later.

It is interesting to note that in contrast to the lethargic encephalitis of von Economo, marked ocular disturbances, such as ptosis and double vision, were quite rare, although slight blurring of vision and even diplopia were occasional transient manifestations at the onset of the disease. Nystagmus and changes in the pupillary reflexes or in accommodation were uncommon. Fundus examination was usually negative.

Among other but less frequent manifestations was paralysis, consisting oftenest of mild or occasionally persistent facial weakness. In other instances spasticity of one or more of the extremities was observed, but such paralytic symptoms as developed usually disappeared within one or two weeks of the onset. Mild exophthalmos was observed in some patients, especially in adults, and in one case was so extreme as to cause complete forward dislocation of the globes. Changes in the pulse rate also occurred, producing such variations as a bradycardia or in other instances a tachycardia. Fever, usually highest in the first few days of the disease, as a rule fell by rapid lysis or even by crisis within eight to ten days of the onset. In exceptional instances, fortunately rare, it persisted of an irregular type, for several months. Improvement usually coincided with the fall in temperature, but occasionally mental confusion or tremor persisted long after the fever had reached normal. Headache and nausea were present only in the early stages of the disease, and vomiting was rarely of a projectile type. Considering the serious nature and situation of the pathologic lesions with their concomitant symptoms, it was amazing to find that most patients had apparently recovered entirely by the end of the arbitrarily determined isolation period of three weeks.

Spinal Fluid: In all types of the disease the spinal fluid as revealed by lumbar puncture was moderately increased in amount and pressure

during the acute stages of the illness. The cell count was increased, numbering as a rule from 50 to 300, or occasionally as high as 500 to 1000 cells, but always predominantly mononuclears. The globulin showed a moderate increase, and the sugar content remained normal or slightly above this level.

Leucocyte Count: The blood count in all types of the disease showed such variations as to make it of little value in diagnosis. As a rule, there was a slight leucocytosis present, but occasionally a well-marked leucopenia was observed. The Schilling hemogram usually showed a slight shift to the left.

Type II.—In this group, the symptoms of encephalitis were preceded by a definite *period of invasion.* During this time, usually one to four days, but lasting occasionally a week or longer, the patient complained of headache, malaise, chilliness or even definite rigors, nausea, abdominal pain, and almost invariably muscular aches in the back and extremities. When it is added that occasionally there was photophobia, and sore throat or other signs of a mild upper respiratory infection, it is not surprising to find that the initial diagnosis in such instances was more likely to be influenza than encephalitis. Moreover, such individuals usually had moderate to high fever, as well as the above mentioned evidences of a generalized infection. During the next few days, however, the temperature fell toward normal and all the symptoms were markedly ameliorated, so that convalescence seemed established. Suddenly, however, the fever again rose abruptly, headache became much worse, and drowsiness, mental confusion, tremors, and nuchal rigidity developed. Thereafter, the course was similar to the Type I infection, the presence of invasive symptoms apparently not affecting the prognosis.

Type III.—In this group are placed the mild or abortive forms of the disease in which the diagnosis would probably never have been suspected but for the fact that there was an epidemic of encephalitis in the community at the time. At best, it seems probable that more such cases were overlooked than recognized. Some degree of fever and headache was ordinarily present, and perhaps transient nausea, chilliness, and abdominal or muscular pains were present. Frequently a slight tremor of hands and tongue, with perhaps absence of the abdominal reflexes, suggested the possibility of encephalitis, although the sensorium was usually clear. Rigidity of the neck or a positive Kernig sign was, of course, of great significance if present. Again, a few patients complained of mild transient vertigo or blurred vision, but drowsiness and mental confusion were slight or entirely absent. Despite these mild symptoms, lumbar puncture revealed typical changes in the spinal fluid. As was to be expected, recovery was very rapid, the symptoms rarely lasting more than a week or ten days. That these were really cases of encephalitis seems amply attested not only by the clinical course and

spinal fluid findings, but also by the presence in the blood of such patients of neutralizing substances for the virus isolated and recognized as the specific cause of the disease.

COMPLICATIONS

These were much more common in adults than in children and increased in frequency and seriousness as the older age levels were reached. Pathologic conditions antedating the onset of the encephalitis (e.g., cardiorenal disease, arteriosclerosis, hypertension), greatly increased the gravity of the disease. The most frequent immediate cause of death, however, aside from the toxemia of the infection, was bronchopneumonia or lobar pneumonia.

PROGNOSIS AND SEQUELAE

As mentioned above, the mortality rate in 1933 was 20 per cent, but in 1937 with a smaller total of cases the rate reached almost 25 per cent. It was lowest in children (slightly over 5 per cent) and rose with advancing age, being markedly influenced by the presence of other pathologic processes which were present at the time of onset of the encephalitis. In nonfatal cases, however, recovery was usually surprisingly rapid and ordinarily complete. Sequelae, such as commonly follow the so-called lethargic type encephalitis, were conspicuous by their absence. In a recent follow-up study of 331 patients of the 1933 epidemic there was found no single instance of definite parkinsonism although 11 per cent had some type of muscular tremor. When it is realized that about 40 per cent of the patients re-examined were over fifty years of age, when tremors from other causes become increasingly common as the age advances, it is evident that this type of sequel is less frequent than was to have been expected from previous experiences with other varieties of encephalitis. It is noteworthy that other organic residual effects actually observed on physical examination were present in but 5.7 per cent of the cases. Forty-two per cent of patients reported no complaints of any nature, but about a similar number reported subjective nervous complaints such as nervous excitability, irritability, headaches, and slight loss of memory. Only rarely were such complaints of a serious nature, and it is significant that they were much less frequent in children than in adults. Indeed, it seems quite probable that in many instances the changes found on physical examination or mentioned as subjective complaints were the result of age rather than the attack of encephalitis. It cannot be gainsaid, however, that in certain instances the central nervous system suffered irreparable damage during the acute phase of the illness, and in consequence permanent sequelae have remained.

TREATMENT

There is at present no specific treatment for acute epidemic encephalitis. Although patients who have recovered from this disease usually have neutralizing substances for the virus in their blood streams, it seems doubtful whether knowledge of this fact will ever prove useful as a therapeutic measure, for once a virus disease becomes established and produces clinical symptoms, specific sera are usually ineffective. Prophylactic injections of such a specific serum would seem scarcely warranted as long as the disease affects only one in a thousand population, as was the case in the St. Louis area.

Lumbar puncture often affords lasting relief from the headache, but further treatment must be entirely symptomatic in the present stage of our knowledge. Especial attention should be given to the prevention of dehydration of the tissues through the use of Hartmann's or Ringer's solution administered subcutaneously and dextrose or sucrose solutions intravenously. Stuporous patients may have to be fed by gavage, although blood transfusions may act as general supportive measures and supply food as well.

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THE EFFECT OF VITAMIN D ON LINEAR GROWTH IN INFANCY

II. The Effect of Intakes Above 1,800 U.S.P. Units Daily

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ALTHOUGH a large quantity of data concerning growth of infants must be analyzed in order to determine standard rates of growth, much can be learned by following carefully the growth rates of small groups of infants, living under carefully controlled conditions of housing and diet. During the past ten years the growth of more than 100 infants has been so watched, many of the infants being studied during the greater part of the first year of life. For a large number of these infants the major differences in the dietary regimen have been in respect to the source and quantity of the vitamin D supplement, changes which necessarily involved also alterations in the vitamin A intake.

The first publication of this series[1] demonstrated that infants given a good diet containing approximately 340 units of vitamin D daily from cod-liver oil,* grew at rates faster than the averages reported in the recent literature.[2, 3] It was shown also that infants given the same dietary regimen but obtaining all their vitamin D from milk containing 135 units to the quart, grew at rates average by the above mentioned standards. These standards, in turn showed rates of growth more rapid than the averages reported in 1920 or earlier.[4] The evidence indicated that vitamin A was not the important factor, and it was concluded that the increased rate of skeletal growth was due to the effect of vitamin D. These findings were subsequently confirmed by Slyker and coworkers[5] in a well-controlled outpatient study of a large number of infants.

The present report discusses factors affecting the interpretation of growth rates of individual infants and extends the study to include a group of infants given from 1,800 to 4,600 units of vitamin D daily.

In a study of a large group, individual variants may be disregarded as being relatively unimportant. In studies of small groups, these variants may lead to erroneous conclusions. For example, it is well known that tall babies tend to grow faster than short ones. A baby 55 cm. long at birth will grow 27 cm. during the first year if his growth is average,[2, 3] but the average increase in length of a baby 45 cm. long at

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This study was aided by grants from Mead Johnson & Company, Evansville, Ind., and National Oil Products Company, Harrison, N. J.
*The term units throughout this article refers to U.S.P. units.

birth is only 22 cm. If the infants of a small group are predominantly either large or small, the growth results must be interpreted accordingly.

Illness also influences the rate of growth in length. In our experience, illness seems always to cause a slowing of growth, but the retardation may be of short or long duration, may occur during the illness, or after the infant has recovered. This period of slower growth is usually followed by a period of more rapid growth, which usually compensates entirely for the earlier slowing. Curves illustrative of these differing effects of illness on growth rate are shown in Fig. 1. The solid lines indicate periods of health, the dotted lines show acute illness, and broken lines a mild middle ear infection. The fine lines represent average growth for infants of the given age. It will be observed that following

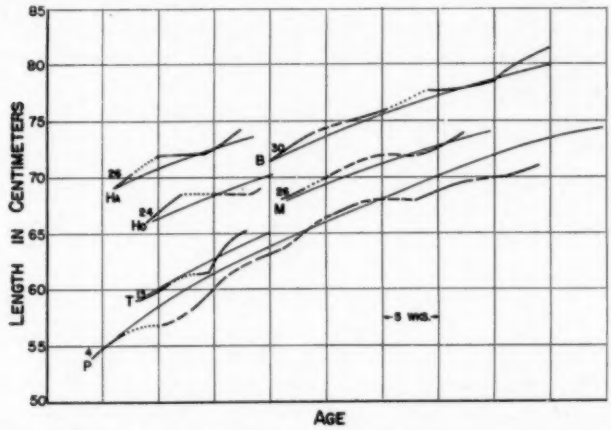

Fig. 1.—The effect of illness upon rate of growth in infancy. The solid lines indicate periods of health; dotted lines, acute illness; broken lines, mild chronic illness, usually otitis media. The age of each infant in weeks is given in numerals at the beginning of the curve, and fine lines represent average growth rate of infants of the given age.

an attack of acute bronchitis of two weeks' duration, the growth of infant Ha completely ceased for a period of four weeks; a similar cessation of linear growth was observed in infant B after acute laryngitis requiring tracheotomy. Both infants subsequently compensated entirely for the temporary slowing of growth. Bronchitis followed by mild middle ear infection caused cessation of growth for six weeks in infant Ho. On the other hand, acute bronchitis in infant T and pneumonia in infant P, both young infants, caused a slowing of growth for only about two weeks, while bronchitis followed by middle ear infection caused little or no slowing of growth until after seven weeks of illness for infant M. The last named infant resumed growth as soon as he recovered from the middle ear infection. The entire growth curve of infant P illustrates the fact that a chronic low-grade middle ear infection may have a far

more marked and lasting effect on the growth rate than a single acute illness of much greater severity. In order to judge the effect of nutrition on the growth of a baby who has been ill, the growth rate should be followed for a sufficient period after illness to include both the compensatory period of more rapid later growth and also a period wherein growth occurs at the baby's normal rate.

Detailed and careful observation of infants under controlled conditions often indicates an apparent lack of relationship between the rate of growth during the first six to eight weeks of infancy and the dietary regimen given the infant. Fig. 2 shows the growth rates of three infants given as the sole source of vitamin D milk containing 135 units to the quart. Curves A and B indicate a steady rate of growth; curve C shows a much more rapid growth rate until the eighth week of life, after which this growth curve parallels the other two. All three infants were given the same dietary regimen throughout. The growth

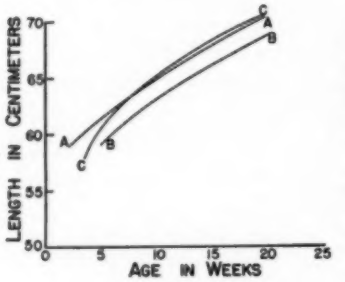

Fig. 2.

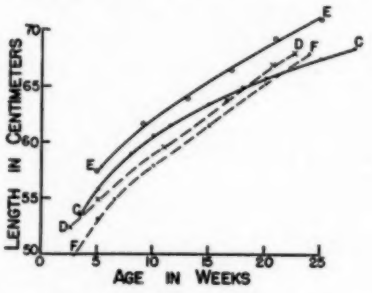

Fig. 3.

Fig. 2.—Growth rates of three infants given milk containing 135 units of vitamin D to the quart as the sole source of the vitamin. The growth rates of all three infants were similar after 8 weeks of age; the rapid earlier growth of infant C indicates the influence of factors other than diet.

Fig. 3.—Growth rate of infant C (Fig. 2) compared with those of three infants given 340 units of vitamin D daily as cod-liver oil. Curves D, E, and F show parallel growth rates after eight weeks, at a rate more rapid than the growth of infant C who received the lower unitage of vitamin D. Curves C, E, and F show rapid early growth, apparently not related to dietary regimen. Curves C and D illustrate the erroneous conclusions which may be drawn when only two measurements of growth are considered; actual rates of growth of the two infants are equal at 18 weeks of age; the growth of infant C is influenced by two factors, that of infant D apparently by only one.

of infant C after eight weeks shows that, throughout the entire period of infancy, his growth rate would probably approximate that of the other two infants. A short term study of this infant, particularly if measurements were taken only at the beginning and end of the study, might lead to very erroneous conclusions concerning the efficacy of the diet.

Fig. 3 shows the growth curve C in contrast to growth curves of three infants given 340 units of vitamin D daily as cod-liver oil. It will be noted that curves E and F show rates of growth previous to eight weeks which are more rapid than during the later period, whereas the growth

rate illustrated in curve D is consistent throughout. After the eighth week, the rates of growth of the three infants given 340 units of vitamin D daily (curves D, E, and F) are very similar and noteworthily greater than the rate of growth of infant C, who was given milk containing 135 units of vitamin D to the quart. A comparison of curves C and D illustrates the error which might easily arise if growth rates of curves C and D were compared only at first measurement and at or near the eighteenth week of life. Such comparison would show equal growth which might be wrongly ascribed to diet. While growth of the two infants is actually equal up to the eighteenth week the growth rate of infant C is the resultant of two factors; that of infant D is apparently affected by only one. Both infants C and F, on the other hand, show rapid early growth. The two curves are approximately parallel to the eighth week, but thereafter the rate of growth depends directly upon the dietary regimen. It seems, therefore, safer when studying growth of individual infants in relation to dietary regimen to consider only the rate of growth after the eighth week of life although the regimen should be instituted as soon after birth as possible.

We are as yet unable to state exactly the cause of these differing rates of growth during the first two months. In the few cases wherein accurate dietary and medical histories of the mother could be obtained, the rate of growth of the infant during the first two months correlated well with the nutritional and physical status of the mother at the time of the child's birth.

In studying the rate of growth of infants given large amounts of vitamin D, the entire growth curve of each infant is presented, but only the part of the curve after the eighth week of life is considered indicative of the effect of diet.

In this study vitamin D was given from three sources, two of which contained also vitamin A. A high unitage cod-liver oil* was given two infants in the amount of three standard teaspoonfuls daily, which allowed an intake of about 1,800 units of vitamin D and 6,300 units of vitamin A. A cod-liver oil concentrate emulsified in cream† was used as the second source; 3 c.c. were added to the daily feedings of each of three infants, permitting a daily intake of 2,200 units of vitamin D and 1,400 units of vitamin A dispersed in the milk. During the last three weeks of the study the vitamin A content of the concentrate was increased tenfold, allowing 14,000 units daily, the vitamin D content remaining constant. Viosterol in oil was given to four babies in amounts allowing about 4,500 units of vitamin D daily; this group of infants received no vitamin A in addition to that of the food. The studies were carried out without regard to season, and during the summer months

*Obtained through the courtesy of Mead Johnson & Company, Evansville, Ind.

†Obtained through the courtesy of the National Oil Products Company, Harrison, N. J.

the infants were outdoors when weather permitted. While the group studied is small in number, the degree of dietary control was excellent, and the growth rates observed differed consistently from those of infants fed 300 to 400 units of vitamin D daily.

The growth rates of the infants are shown in Figs. 4, 5, and 6 in comparison with the Kornfeld standard curves as background. Fig. 4 shows the linear growth of two girls, one given cod-liver oil (1,800 units of vitamin D daily), and the other viosterol (4,600 units of vitamin D daily). Neither child showed extremely rapid growth during the first two months; both grew consistently faster than the average rate until 20 to 25 weeks of age. At that age a short period occurred wherein growth ceased entirely, after which linear growth was resumed at a rate

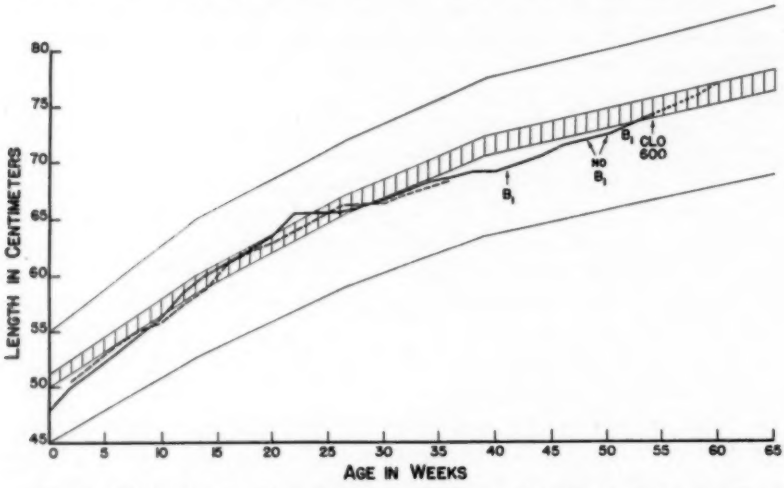

Fig. 4.—Linear growth of two girl infants given very high vitamin D dosage. The fine lines represent the average rates of growth by the Kornfeld standard. Baby B received 1800 units daily as cod-liver oil; Baby S was given 4600 units a day as viosterol. The period B_1 marks the term of thiamin therapy. The dotted line shows the growth rate when the vitamin D dosage was decreased to 600 units as cod-liver oil; rate of growth increased. (Broken line, Baby B; solid line, Baby S.)

below the average normal. Infant S who received viosterol was studied under this regimen until 40 weeks of age. As some decrease in appetite had been observed, thiamin (vitamin B_1) was added to the daily diet in the form first of an extract of rice polishings, later in a form combined with the carbohydrate (a dextrin-maltose mixture) of the milk feeding. Some increase in growth rate followed, but as both forms of the vitamin addition proved laxative, necessitating rest periods, the use of the thiamin addition was discontinued and the vitamin D dosage was changed to one teaspoonful of cod-liver oil, containing about 600 units of vitamin D. Growth was maintained at greater than average rate for a period of six weeks, when the study of the infant was concluded.

The second infant (B) whose growth rate is shown in Fig. 4, was given three teaspoonfuls of cod-liver oil daily, permitting an intake of 1,800 units of vitamin D and 6,300 units of vitamin A. This infant also showed evidence of decreased growth after about 6 months of age. The study of baby B could be continued only until the thirty-sixth week of age; the feeding instructions at discharge allowed only one teaspoonful of cod-liver oil daily. The baby visited the ward on her first birthday. At this age she was considerably taller than baby S., who was the same age. As will be seen from the chart, the two were of almost identical height at 36 weeks of age. The rate of growth of baby B, therefore, must have been above normal after the vitamin D dosage was decreased.

Four other girl infants have been studied (Fig. 5), but only one could be studied throughout the major part of infancy. This infant (Sa) had been used as a subject for a study of the effect on growth and

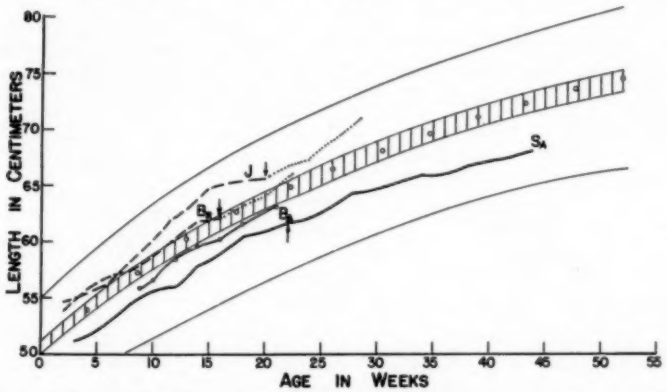

Fig. 5.—Linear growth of four girl infants given very high vitamin D dosage compared to standard Kornfeld rate. Dotted portions of curves represent growth rates observed when the vitamin D dosage was decreased to 400 units daily as cod-liver oil. Babies Br and J were given 2200 units of vitamin D daily as the cod-liver oil concentrate dispersed in the feeding; growth increased when the dosage was decreased to 400 units daily. Baby Ba was given 4600 units daily as viosterol. Baby Sa was given 270 units daily as viosterol until 21 weeks of age, at which time the dosage was increased to 4600 units. The slowing of growth with high dosage contrasts with the increase of growth rate of baby J when the vitamin D intake was lowered. The circles represent average lengths observed by Peatman and Higgons[4] for girl infants given 1600 to 9000 units of vitamin D daily.

mineral retention of a vitamin D intake of 270 units daily as viosterol. That study had been discontinued in the spring and the baby, then 21 weeks old, was thereafter given 4,600 units of vitamin D as viosterol. The rate of growth to 21 weeks had been average; after this period, the rate was considerably below average, remaining so throughout the study. The failure of the high vitamin D dosage to increase growth rate is in contrast to the increase in growth rate noted in baby S when 600 units of vitamin D were substituted for 4,600 units.

Baby Ba was given 4,600 units of viosterol daily from the date of her admission at the age of 9 weeks. At 21 weeks, the baby left the hospital.

Growth was about 1 cm. greater than the average rate and had not yet showed evidence of slowing, a result similar to those observed with infants S and B at the same age.

Two girl infants were given the "high vitamin D milk" made in the laboratory by adding to each day's feeding enough cod-liver oil concentrate dispersed in cream to give a total day's intake of 2,200 units. These infants could be studied for less than six months. No decrease in appetite was observed. One infant, Br, grew at a little less than average rate at the beginning of the study, and at average rate after the age of eight weeks. The growth of the other baby, J, was faster than average from the eighth to the fifteenth week, then showed a definite slowing for the succeeding five weeks. The vitamin D intakes of both infants

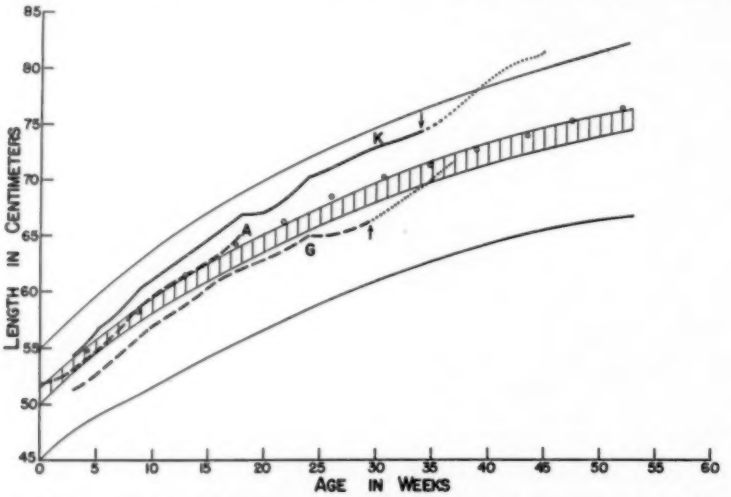

Fig. 6.—Linear growth of three boy infants given very high vitamin D dosage compared to standard Kornfeld rate. Dotted portions of curves represent growth rates observed when the vitamin D dosage was decreased to 400 units daily as cod-liver oil. Baby G received 2200 units daily as the cod-liver oil concentrate dispersed in the feeding; Baby A, 1800 units daily as cod-liver oil; and baby K, 4600 units a day as viosterol. The rates of growth of babies G and K were increased when the vitamin D intake was decreased to 400 units a day. The circles represent average lengths observed by Peatman and Higgons[6] for boy infants given 1600 to 9000 units of vitamin D daily.

were then changed to 400 units daily as cod-liver oil. Subsequent growth is shown as dotted lines. Baby J showed average growth for four weeks, then sharply accelerated growth for the succeeding four weeks. Baby Br's growth was maintained at average for four weeks, and then the rate increased somewhat.

The growth rates of the three boy infants are shown in Fig. 6. The lowest curve, G, indicates the growth of the baby given 2,200 units of vitamin D in the milk, as the cod-liver oil concentrate dispersed in cream. Growth proceeded at better than normal rate until 16 weeks

of age and from then to 24 weeks at barely normal rate. After the twenty-fourth week growth was definitely slowed. At 29 weeks of age the high vitamin D feeding was discontinued, and 400 units of vitamin D as cod-liver oil were given daily. The growth rate showed an almost immediate increase, which was maintained for a period of six weeks, until the study was concluded.

A second boy, A, was given 1,800 units of D daily as cod-liver oil. This baby left the hospital at 18 weeks of age, before any slowing of growth was observed. The child's appetite was excellent throughout the study.

The third boy, K, was remarkable for his excellent appetite throughout the entire study. His food intake was always above average. His rate of growth was excellent up to 24 weeks of age, except for one temporary slowing due to an upper respiratory infection. From the twenty-fourth to the thirty-fourth week growth continued at average rate. Slowing of growth in this child could not be considered as due to decreased ingestion of food caused by lack of appetite. The child's hands and feet were very large compared to his body size, so that, even though the baby's length was above average, it was felt that stunting might have occurred. The vitamin D dosage was therefore decreased to 400 units daily, given in the form of cod-liver oil. After two weeks the growth rate increased, and in ten weeks the body length had increased 6.6 cm. or 3.2 cm. above the expected increase of 3.4 cm. in this period.

Summarizing, each infant given the high D dosage and studied up to 25 weeks of age or longer showed a slowing of growth to or below average rate by the standard used. Each of these infants who was then given a lower dosage of vitamin D, 400 to 600 units daily, showed an increased rate of growth, four of the five growing at markedly greater than average rates for periods of four to ten weeks.

In some of the infants the decrease in rate of growth observed when the very high dosage of vitamin D was given could be ascribed to decreased appetite with consequent food refusals; other infants, however, showed excellent appetites throughout the study, but the growth rate could still be increased by decreasing the daily vitamin D ingestion. The depression of appetite occurred as often when the vitamin was given in concentrated form, as when it was ingested as three teaspoonfuls of oil.

Four infants were given no vitamin A in addition to that of the food; of these, two grew at less than average rate and one at average rate during later infancy, while the study of the fourth was concluded at twenty-one weeks, at which time she was growing at average rate. Two of these babies were later given cod-liver oil containing 400 and 600 units of vitamin D, 2,800 and 4,200 units of vitamin A, respectively. Both babies showed a definite increase in rate of growth.

Two babies were given three teaspoonfuls of cod-liver oil, containing 12,000 to 13,000 units of vitamin A in addition to that of the food. One baby grew at less than average rate after 25 weeks of age; at 34 weeks of age the cod-liver oil dosage was decreased to one-third of its former level, thus decreasing the intake of both vitamins A and D; growth proceeded more rapidly. The second infant was studied only to 18 weeks of age; the rate of growth was above average at that age.

Three babies were given 1,400 units of vitamin A daily in addition to that of the food. During the last few weeks of the vitamin D study the vitamin A content of the diet was increased tenfold, the vitamin D ingestion remaining constant. The growth rate of two of the three infants continued to decrease, that of the third remained approximately the same. When the vitamin D intake was decreased to 400 units daily and the vitamin A intake to 2,800 units, the rate of growth increased for all infants.

Of the five infants studied to thirty weeks or later, four presented a very definite slowing of growth, one grew at average rate. The infant who grew at average rate and two of those whose growth rate was below average received no vitamin A in addition to that of the food. One infant whose later growth was below average, received 6,300 units of vitamin A in addition to the vitamin D; her rate of growth was practically identical with that of one of the infants given no added vitamin A. The fifth infant was given a tenfold increase in amount of vitamin A for three weeks of the study without any observable increase in growth rate occurring, in contrast to the prompt increase in growth rate when the vitamin D intake was lowered. Thus, the slowing of growth, when observed, was noted in infants given additional vitamin A or only that of the diet. The increased rate of growth which followed the lowering of the vitamin D intake occurred whether the vitamin A intake was lowered markedly or increased. Vitamin A, in amounts above those supplied by the food, apparently does not affect linear growth in infancy.

The study of these nine infants indicates that when vitamin D is fed to infants in amounts over and above 1,500 units daily, growth proceeds at average or greater rate up to about 6 months of age, and that after 6 months of age, increase in length occurs at average or less than average rate. The rate of growth with very high vitamin D dosage is thus about the same as had been observed for sixteen infants given vitamin D milk containing only 135 units to the quart, and is definitely slower than the growth rate observed in thirty-six infants given 340 units of D daily.

Very similar results in growth rate with high vitamin D intake are reported in a large outpatient study by Peatman and Higgons.[6] These authors report growth rates of 1,112 subjects (577 boys and 535 girls)

of whom 60 per cent came from the middle or wealthy classes. The infants were of American parentage, with northern European stock predominating. The dietary regimen was very carefully supervised and included vitamin D as follows: "Cod-liver oil or one of its substitutes is started at four weeks. By two months each child receives daily 9,000 or more units of vitamin A (U.S.P. XI) and 1,600 or more units of vitamin D (U.S.P. XI). At 4 months this dose is increased to a minimum of 20,000 units of vitamin A and 3,200 of vitamin D. After 8 months the amount varies from this minimum to a maximum of three times this quantity, depending on the condition of the child."

The average lengths observed by these investigators are shown in charts 5 and 6 as circles. It will be noted that the average growth rate for the boys is almost identical with the "upper average" line of the Kornfeld standard, and for the girls, exactly average according to the standard. That average growth was achieved by the outpatient group and less than average growth was observed for many of the infants of the present study may be attributed to the better degree of control always possible in inpatient studies. The data presented by Peatman and Higgons thus support admirably the data presented in this paper.

The effect of vitamin D on linear growth apparently reaches a maximum and further increases in intake result in decreased, rather than increased rates of growth. The rate of growth of infants given 135 unit vitamin D milk is greater than that of infants given no vitamin D;[1, 5] infants given 340 units[1] or 600 units[5] of vitamin D daily grew at noteworthily greater rates than those receiving only 135 units. No definite difference in growth rate appeared between the groups given 340 and those given 600 units of D daily. Infants given very high dosage of vitamin D (1,800 to 5,000 units daily), however, grew at rates definitely less rapid than those given 340 to 600 units, and approximately equal to those of the group fed milk containing 135 units to the quart. A few infants given these high dosages grew no faster than infants receiving no additional vitamin D.[4, 5]

This study of growth of infants with a high intake of D brings out an additional factor which must be considered in studying the growth of individuals, namely, that some factors of diet definitely affecting growth may not show a noticeable effect until the infant is more than 6 months of age. In order to determine the effect of a given dietary regimen upon the rate of growth and development of the infant, it appears necessary to study the infants throughout the greater part of the first year of life.

SUMMARY

The rate of linear growth of nine infants given from 1,800 to 4,600 units of vitamin D daily has been compared with standard rates of growth, and with the growth of infants given the same dietary regimen

but amounts of vitamin D varying from 135 to 340 units daily. The rates of growth with the very high vitamin D intake were similar to or less than those of infants given 135 units daily, and definitely lower than the growth rates of infants given 340 units of vitamin D daily.

It is concluded that the effect of vitamin D on increasing linear growth reaches a maximum when the vitamin D intake is greater than 135 and less than 1,800 units, probably in the neighborhood of 340 to 600 units daily.

Vitamin A in amounts exceeding those of the food (milk, vegetable, and fruit purées) apparently does not affect linear growth of infants.

Factors affecting growth rates of individual infants are discussed. It is concluded that in order to determine the effect of the dietary regimen, growth should be studied well past 6 months of age, preferably during the greater part of infancy. Growth during the first 8 weeks of life may be affected by factors other than the dietary regimen of the infant.

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ENCEPHALITIS RHEUMATICA
(CHOREA MINOR OF SYDENHAM)

Its Diagnosis and Course

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Introduction.—Chorea continues to be a disease of great pediatric interest and discussion because of its frequency of occurrence and its uncertain etiology and relation to rheumatic fever. Because of the nature of the condition there is great difficulty in securing direct evidence of its cause, course, and relationship. It is the purpose of this paper to discuss, first, the concept of the disease formed from an experience during the past twenty years at the St. Louis Children's Hospital, in the Children's Cardiac Clinic, and, second, to describe the common conditions occurring in pediatric practice which simulate the disease and may be confused with it.

Dr. Marriott was always interested in each case of chorea on the wards and stimulated others about him in the subject. Probably the elusive, unknown, uncertain features challenged his scientific mind to search for something new.

History.—Since Sydenham's original description of chorea[1] in 1686, very little important information has been added. Cheadle[2] pointed out clearly and definitely the close relationship between chorea and rheumatism in children and probably was the first to emphasize the peculiar manifestations of rheumatism in children as compared with adults. His description of chorea supplements Sydenham's with accurate clinical observations based on principles of modern medicine. Since Cheadle's work nothing has been added to our knowledge.

Pathologic reports are extremely meager, there being no mention of the disease in most text books of pathology. Clinical studies and reports of importance during the past twenty years come from either neurologists and psychiatrists,[3-6] with emphasis on the symptoms and relation to other types of incoordinate movements of children, or from pediatricians,[7, 8, 9] and cardiologists,[10-13] with more emphasis on the relation of the disease to the rheumatic state and its manifestations elsewhere in the body. These reports describe less the symptoms and more the underlying cause of the disease, the widespread lesions of rheumatism in children, and the high incidence of heart disease in the general group. Many of these reports are concerned with the direct relationship

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Presented in part at the joint Meeting of Regions II and III, American Academy of Pediatrics, in St. Louis, Nov. 18, 1935.

between chorea and rheumatic heart disease in children. Most of the general literature is concerned with the treatment of the disease, and in this connection reference may be made to Sydenham's original statement that "purging and *alternating medicine* are to be used until he [the patient] is quite well." And from the current literature, it is apparent that there seem to be many alternative remedies.

Clinical Picture.—The clinical appearance of children with chorea is well known generally. There is a history of gradual onset of several days or weeks of "nervousness," or "twitching," or "irritability" and "peevishness," or "being tired," and irregular movements occurring during the waking hours, of all parts of the body under voluntary control. The severity of jerking and incoordinate movement progresses in degree together with appearance of a more or less marked emotional instability and imbalance characterized by irritability, more often crying, less often laughing about irrelevant details. All the semivoluntary functions, such as speech and respiration, may be involved to some degree. There may be such incoordination as to simulate paresis of a limb or part. Not only does the child make purposeless, aimless, involuntary movements, but there is a great degree of incoordination and confusion of purposeful movements. These movements show no intention intensification. They are never present during sleep, which is usually undisturbed though restless. Due to difficulty in feeding and walking, there is loss of weight and malnutrition after the first few weeks. There is usually a history of acute rheumatism, either a previous attack of chorea or some other rheumatic manifestation, such as arthritis, heart disease, or tonsillitis. Often an upper respiratory infection has preceded the onset of the chorea, though this may be so insignificant as to escape notice. A history of fright or some other emotional strain can be obtained usually, though logically a mental shock may be only the first consciousness of the family that the child is "nervous." In all probability the emotional strain is the result rather than the cause of the attack of chorea.

The attacks are more frequent in girls than boys; more frequent in the spring of the year than at other times; commoner in older children than younger children; commoner in blonds than in brunets; and commoner in children with frequent "colds" and "sore throats." All races seem equally affected when living under the same conditions. The Negro race[14] in the northern cities, is particularly subject to chorea as a manifestation of rheumatism. The patient's mental and emotional development varies, and it may be said that chorea develops only in those children who have some weak point where the manifestation starts. The familial socio-economic background is generally faulty and furnishes a fertile soil for emotional disturbances to appear. The intelligence quotient determined in choreic children may be low or high but is usually an irregular curve, independent of performance tests based on

muscular coordination. It has been shown by many workers, that rheumatism is increasingly frequent in the lower social strata, particularly when the family is impoverished in ability to make the best of poor circumstances or to provide proper health and environmental facilities for their children. This implies an intellectual poverty as well as an economic poverty. Chorea may be an exception to this feature of rheumatism, for one is likely to encounter chorea rather frequently in private practice.

Few positive, objective findings can be observed in a child with active chorea. There is no fever; the blood picture is usually normal, though eosinophilia of 5 to 10 per cent has been found in a surprising number of children. There is no leucocytosis, but the sedimentation rate of red blood cells may be prolonged.[15] Findings in the heart as well as changes in other parts are a concurrent result of rheumatism. The neurologic examination is normal except for the movement. The reflexes are inconstant, but in no way suggest an anatomic lesion of the brain or spinal cord. No satisfactory explanation has been offered for the movement of the body which could be caused by the known changes in the brain. The pattern of the movement at no time is constant as in paralysis agitans, nor does the movement suggest a chorea major (Huntington's chorea). X-rays, spinal fluid examinations, and chemical studies of the blood and body tissues have shown no consistent changes. The basal metabolic rate when determined before or after the period of chorea is normal, and there is no other evidence of internal gland disturbance.

Brain specimens examined postmortem are rare since the patients usually recover. Specimens which have been described show increased vascularity, a few plasma cells scattered irregularly, and slight edema of the glial structures. These changes may be found generally but are located chiefly about the basal nuclei. No structures resembling rheumatic nodules have been described, and no changes suggesting scar tissue formation have been seen. These findings, even in the few cases, seem important in that they are characteristic features of rheumatic fever found elsewhere in the body, especially in the joints. It is also well known that rheumatic nodules are not often found in children about the joints or elsewhere during an attack of acute arthritis with periarticular swelling. These observations should serve to classify the disease as one of the exudative manifestations of rheumatic fever, rather than as a proliferative one. When the proliferative changes occur, there are invariably scars resulting in the tissue in which the nodules occur, such as the heart. This is probably the explanation of why chorea is not followed by permanent paralysis, weakness, or other neurologic changes in the body or brain.

In this respect too, there are essential differences from other types of encephalitis where permanent damage to brain tissue is the rule in many cases. But the same findings occur in the joint when one con-

trasts attacks with acute rheumatic fever, with either chronic rheumatoid arthritis in children (Still's disease) or in adults. In both of these conditions there are progressive structural changes in the joints, involving periarticular tissue as well as cartilage, bone, and joint capsule. The changes in the brain in chorea, therefore, represent a type of inflammatory process or a response of that tissue to the agent of rheumatic fever and should be classed as a true encephalitis.

Chorea patients usually recover completely without residual injury of any kind. After several weeks a slow improvement is noted, and the symptoms disappear. The recovery may be spontaneous, occasionally may occur rapidly, or may result from the many available forms of therapy. If the rheumatic process progresses in other parts of the body, especially the heart, the picture changes. Reoccurrence is frequent, especially during the spring season, or the next manifestation of the rheumatic process may be in some other region.

Differential Diagnosis.—Among the conditions occurring in children, chorea must be distinguished from poliomyelitis, encephalitis lethargica in its several forms, psychogenic motor disorders, hysteria and habit spasms, occasionally brain injuries and tumors, and from physiological myxedema of adolescence.

Children with hemichorea often suggest poliomyelitis when the incoordination is so pronounced as to interfere with walking, or the use of the arms and legs. The differential diagnosis is easy to make as there are neurologic findings of importance in poliomylitis, such as nerve trunk pain, changes in reflexes, and objective weakness of the affected part. In all doubtful cases spinal fluid examinations should be made to establish the diagnosis.

Encephalitis lethargica, in its early stages, may resemble chorea because of the delirium, confusion, incoordination, and weakness. The rapidly progressive course of encephalitis lethargica tells the story in a day or so. Fever, slight leucocytosis and lymphocytosis, the absence of eosinophilia, and the organic neurologic findings are observed in the acute cases of encephalitis lethargica, and the examination of spinal fluid makes the diagnosis.

It has been suggested that choreiform movements may occur in children as a late result of an attack of encephalitis lethargica so mild as to be missed at the time; or an attack of encephalitis of a milder form, such as the St. Louis type, or a postinfectious encephalitis following measles, whooping cough, chicken pox, or mumps. In the latter group there are many children who may have a mild encephalitic change at the time of the initial disease, who later develop encephalitis recognizable at the time, or the changes may be delayed for months or years. It has been the observation in this clinic that numerous children, with so-called idiopathic chorea in the absence of history or findings of rheumatic fever, give a history of a severe attack of one of the children's contagious dis-

eases or a combination of several in rapid succession. Such children are usually in the younger age group, from 6 to 10 years.

Psychogenic motor disorders offer the most frequent, difficult differential diagnosis. Among adolescents, especially girls, hysteria may simulate chorea closely, and considerable examination may be required to distinguish the two conditions. Habit spasms in the younger age group must be distinguished, but there is rarely any difficulty. The pattern of the habit spasm is constant, though the pattern may change from one to another. Habit spasm is usually limited to an affected part, and there is no emotional disturbance and no other signs of rheumatic fever. Habit spasms last for a longer period of time, are often imitative, are contagious, and have a purposeful, even though misdirected character.

We have also observed choreiform movements frequently in children with crossed cerebral dominance, as described by Orton and other workers. The history of reading and spelling difficulties, especially disturbances of speech, crossed handedness and eyedness, most apparent in the early school age, together with emotional disturbance at home and behavior difficulties should suggest the psychic nature of the choreiform movement and serve to distinguish these children from those with rheumatic chorea.

Careful neurologic examination will reveal sooner or later the presence of tumors and of brain injuries at birth and subsequently, though these findings should be suspected in all cases of chorea even of known rheumatic origin.

We have observed, in increasing numbers in the older age group of 10 to 15 years, children with choreiform movements who have body pains especially in the legs at night; school difficulties, especially a slight but definite deterioration in the quality of school work, usually in the spring of the year; lack of appetite; an increasing laziness both mental and physical; a definite tendency to obesity; a retardation of linear growth with increasing gain in weight; a slightly lowered basal metabolic rate, and a progressive myopia. Such children have what has been termed "physiologic myxedema of adolescence," and on administration of thyroid gland substance these signs and symptoms quickly respond and disappear. The choreiform movement which these children manifest is indistinguishable from true rheumatic chorea. The story of body pains also makes the differential diagnosis somewhat difficult. However, the absence of objective joint signs, the occurrence of pain at night and only in the legs, and the ill defined nature of the pain serve to classify them. Careful consideration of the clinical picture of this type of adolescence disturbance and the absence of psychogenic factors and rheumatic history or findings should point the way. The similarity of the two groups of cases is striking, and repeated examinations are necessary.

It is probably true that every child with chorea has some lowered resistance of a structural somatic defect in the portion of the brain which gives rise to choreiform movements and that the associated occurrence of an etiological factor only serves to bring to light the encephalitic injury. This injury or change in the brain must determine the incidence of chorea in rheumatic children since only a portion of such children develop chorea. There has been no evidence that the agent of rheumatic fever, toxin, virus, or bacterial product of any nature, has a neurotropic quality other than a general affinity for all endothelial tissue of highly specialized function.

Relation to Rheumatic Fever.—It has been implied throughout this discussion the chorea minor of Sydenham is a rheumatic manifestation, and it is believed in this clinic that such is the case. For this reason the term *encephalitis rheumatica* is suggested as proper and more descriptive. It should serve to distinguish such cases from all others with a more obvious etiology or from those with idiopathic chorea of unknown etiology. Since the attack of chorea may be the first manifestation of the rheumatic state in a child, all cases must be watched for further or the later development of the usual picture of rheumatic fever. Also the usual number of rheumatic children may have the factors described above to cause the development of chorea and likewise children with chorea due to those same factors mentioned above may develop rheumatic fever. Therefore, there will always be a certain overlapping in the diagnosis of all children.

It would be difficult to estimate in any statistical way, the relationship of chorea to rheumatic fever. Clinical observations of large groups of children with either rheumatic fever or chorea show strikingly a close relationship. The lack of anatomic observations on brain tissues results from the nature of the situation, the lack of opportunity to secure brains for examination at autopsy, and from the inaccessibility of the brain for any examination other than an indirect one. The unknown nature of the etiologic agent of rheumatic fever makes it impossible to carry out tests or experimental studies for the classification of chorea. It is suggested that the encephalitis of rheumatic fever is similar in its anatomic process to the arthritis, the acute pericarditis, and myocardial changes of an exudative attack of rheumatic fever. The erythemas and urticarias of rheumatic fever are of this same order. The occurrence of an attack of chorea following an acute upper respiratory infection, or tonsillitis, in the same way attacks of other manifestations of rheumatism occur, also should serve to emphasize the causal relationship.

CONCLUSION

The term *encephalitis rheumatica* is suggested for chorea minor of Sydenham in order to emphasize the relationship of chorea to rheumatic fever and to describe the nature of the process in the brain. It is sug-

gested that encephalitis rheumatica (chorea) is an exudative manifestation of the rheumatic state. The nature of the lesions in the brain in this type of encephalitis is similar to those occurring in the joints, heart, and other parts of the body.

Careful study of all cases of encephalitis rheumatica should be made to distinguish them from brain injuries and tumors, from encephalitis due to other causes, especially postinfectious encephalitis of childhood, from psychogenic motor disorders of children and adolescents, and from physiologic myxedema of childhood.

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THE IRREGULAR EXTENSIONS OF THE END OF THE SHAFT IN THE X-RAY PHOTOGRAPH IN CONGENITAL SYPHILIS, WITH PERTINENT OBSERVATIONS

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THE x-ray changes at the ends of the long bones in congenital syphilis are subject to great variation. Actual changes in the bone may be too slight to show in the x-ray picture. On the other hand, they may be so developed as to disfigure and deform the x-ray image to an extent not equaled in any other disease. Moreover, they vary greatly in kind. Either the *Spirochaeta pallida* must be subject to variation in its growth requirements, or bones in different infants must vary much in their different parts with respect to growth favorableness, or circulatory conditions must vary. At any rate, in some infants it is the cartilage cells which seem to bear the brunt of the invasion, and in others it is the osteoblasts which are especially affected; in some destructive processes appear as the predominant feature, in others an irregular new bone formation in the periosteum. In this article, which is presented as a very small token of respect for the memory of Dr. McKim Marriott, who exerted so powerful an influence in pediatrics in this country and abroad, we call attention to an x-ray phenomenon of congenital syphilis which in some cases is very striking. We refer to the irregular projections of the dense shadows of the end of the shaft into the cartilage which give to the end such a jagged appearance in the x-ray film. What is their cause? This is the question which we shall answer. Before we do that, however, it will be necessary to describe in some detail the vascular supply of the epiphyseal cartilage, the cartilage canals, and the changes produced in them by syphilis, and also to make clear the changes in the cartilage itself produced by the disease, since the formation of the projections is dependent on them. Inasmuch, also, as the projections seem to vary with the rate of growth, not only in different bones but in the skeleton as a whole at different age periods, it seems advisable to say something on that subject.

The irregular projections of the end of the shaft into the cartilage are not always present in congenital syphilis. They are usually absent if the syphilitic involvement is slight, and they may be absent, even though the involvement is extremely severe. When the condition is well developed in a long bone of an extremity, the end appears jagged, irregularly serrated, or marked by wedgeshaped, thornlike, or completely irregular projections; in some instances it looks irregularly scalloped

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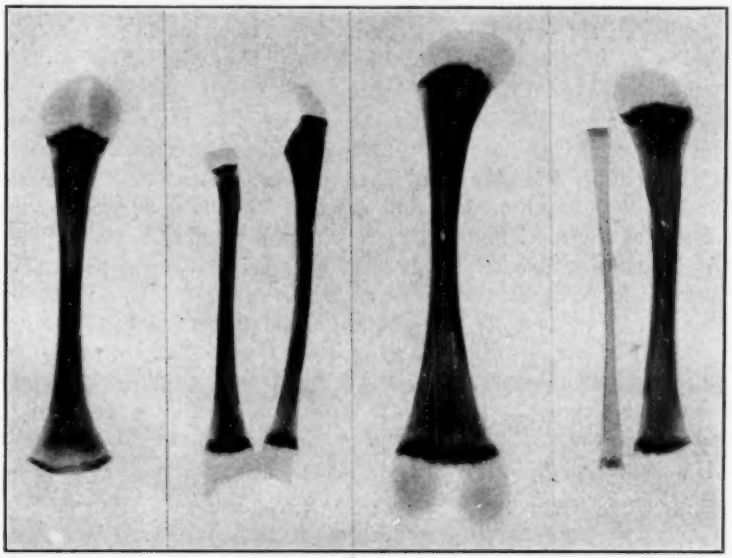
(Figs. 1 and 2). In the ribs the picture is somewhat different. The extensions into the cartilage are longer and sharper (Fig. 3). The



A. *B.* *C.* *D.*

Fig. 1.—X-ray photographs of the humerus, radius, ulna, femur, tibia and fibula taken from Baby T., No. 599, stillborn. The ends of the bones show the characteristic projections with which this paper deals. Notice that they are absent at the slow growing ends of the upper ulna, upper radius and lower humerus.

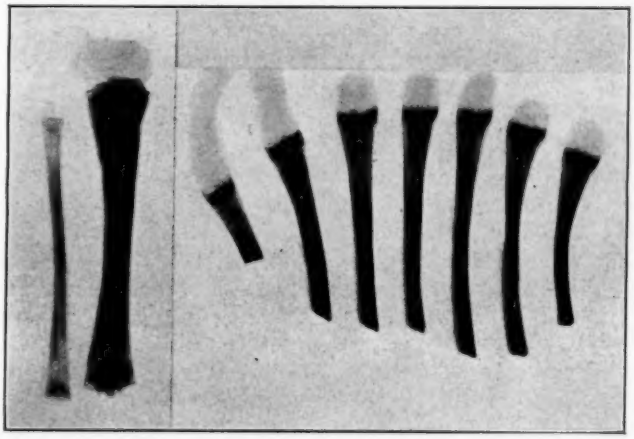


Fig. 2. Fig. 3.

Fig. 2.—X-ray photograph of the tibia and fibula of a syphilitic infant, Baby B., No. 300, aged 6 hours. The ends show a scalloped type of irregularity.

Fig. 3.—X-ray photograph of the middle tier of ribs taken after death from I. N., No. 517, aged one day, showing a sample of the kind of changes at end of ribs which occur in congenital syphilis.

appearance is often as if the rib were barbed or pronged. Whether rib or long bone of the extremity, the end appears to be abnormally dense and the prolongations under discussion seem to have the same density as the end. The impression is obtained that some abnormal formation occupies the end of the bone and that it is this which juts out irregularly into the cartilage.

An analysis of the x-ray films in our series of cases of congenital syphilis, exhibiting the phenomenon, shows that the bone ends most commonly affected are the rapidly growing ones. The slow growing ends do not show it at all or do so indistinctly. The almost stagnant upper end of the ulna does not develop it; the upper end of the radius may show it occasionally. The lower end of the humerus shows it rarely, though at the same time it may be extremely developed at the fast growing end. In general the development is in proportion to the rate of growth. For this reason in our series it was greatest at the anterior ends of the middle ribs, next at the lower end of the femur, next at the upper end of the femur, both ends of the tibia and the upper end of the humerus, and next at the lower ends of the radius and ulna.

But the relationship to growth rate is not a constant one, as in certain other conditions, and ceases to be clearly evident soon after birth. Rickets, which is a disturbance in metabolism, involves the ends of the long bones in exact proportion to their rate of growth. As might be expected, the heavy metals which form insoluble compounds with phosphates and at the same time happen to cast shadows in the x-ray film, for example, lead, are deposited at the ends of the bones exactly according to the rate of growth. Elementary phosphorus, which stimulates bone production and causes shadows to appear in the x-ray film solely by increasing the density of structure of the bone, also affects the ends of the long bones exactly in proportion to their rates of growth. One can actually measure the abnormal bone produced under the influence of rickets or during the administration of the metals and in that way determine the growth rate. One would scarcely expect that congenital syphilis, a disease produced by living things which move about and multiply according to various conditions of vascularization and tissue favorableness, would manifest itself in the skeleton symmetrically or according to any growth scheme. Nevertheless, it is true that in fetal syphilis the affection of the ends of the bones is in general proportional to the rate of growth. Indeed, by actual measurement of the depth of the syphilitic formations in stillborn children it can be demonstrated that the upper end of the ulna grows relatively faster during intrauterine life than after birth. After birth has occurred, the bones are no longer affected by congenital syphilis according to the rate of growth. Why this is so, we do not know, but we surmise that factors coming into being with extrauterine existence, such as trauma, muscle strain and strain resulting from gravity, all become operative, alter the vascularity or other

conditions and predispose toward the lodgement, multiplication and activity of the spirochetes in them. The closer, then, to birth, the greater the approximation of involvement of the ends of the bones to the rate of growth. The older the infant, the less the correspondence, until there is none at all. In our analysis of 77 cases of congenital syphilis, in which the bones were studied both by means of x-ray and histologic methods, the phenomenon was noted 48 times. In 20 instances the infant was stillborn and in 18 was 2 weeks of age or under. When the syphilis makes its appearance at the ends of the long bones for the first time at the end of the first or second month, the phenomenon does not usually develop. The oldest infant showing it, however, was 6 months of age, so there are exceptions.

Growth in length occurs faster in fetal life than ever again. Inasmuch as growth in length depends on proliferation of the epiphyseal cartilage, it would seem probable that the phenomenon under discussion was connected with the rapid growth of the cartilage and that its occurrence chiefly in connection with intrauterine syphilis is explicable on that ground. Indeed, it is in the infections already well developed at the time of birth that one finds the widespread affections of the cartilage presently to be briefly described.

When one studies the bones of congenital syphilitics after death in order to ascertain the cause underlying the x-ray phenomenon, one finds that the projections are about the nutrient vessels of the cartilage, known as the cartilage canals, and that in many instances the proliferative cartilage itself shows extreme degenerative changes. It seems likely that the two phenomena are related. First, then, what are the cartilage canals and what is the effect of the disease upon them and, second, what are the degenerative changes in the cartilage produced by the disease?

The cartilage canals (Fig. 4) are the nutrient vessels of the cartilage *plus their connective tissue sheaths*. The connective tissue sheaths are very thick and make the canals appear as large structures. The sheath probably acts as an insulation, protecting the cartilage from the direct contact with the blood. In the specimen cleared with oil of wintergreen, so that both cartilage and connective tissue become transparent but the outline of the vessels still remains visible often by virtue of their contained blood, the canals appear as tunnels in the middle of which lie the artery and entwined about it one or two veins. The blood vessels are branches of the perichondrial network of arteries and veins. The arteries enter from all sides. It is as the result of this penetration that the interior of the epiphyseal cartilage becomes vascularized and the nucleus of ossification of the epiphysis forms. The canals persist only for a time which varies with the particular bone. But we are interested only in the cartilage canals which supply the generating zone of the proliferative cartilage and shall limit our descriptions to them.

In the ribs and certain other long bones (but not in the femur) the vessels which form the nutrient supply of the proliferative cartilage penetrate the perichondrium and enter the resting cartilage just on the distal side of the generating zone of the proliferative cartilage. They run perpendicularly into the cartilage along the distal surface of the generating zone and converge toward the center. Before arriving at the center, however, they end and, before ending, give off branches which descend a short distance toward the shaft. They are end vessels, not anastomosing with each other or with the vessels of the shaft. Occasionally it happens in the normal bone that a branch of a cartilage canal

Fig. 4.—Drawing from the upper end of the femur, cleared in oil of wintergreen, to show the relationship of the cartilage canals to the projections from the end of the shaft. When a canal approaches the end of the shaft, the shaft seems to mound up or ridge in order to meet it.

directed toward the shaft may be very large and may even reach the shaft. However, this is a rare exception. Undoubtedly the function of the cartilage canals lying along the generating zone of the proliferative cartilage is to supply nutrient material to it. As long as growth in length lasts, the cells in the generating zone keep multiplying, just as the epithelial cells in the basal layers of the skin keep multiplying throughout the life of the individual. It is as a result of the multiplication of the cells in the generating zone of the proliferative cartilage that the bone grows in length. It is natural, therefore, that it should have a special nutrient supply. The vessels in the cartilage canals seem to end

in bulbous terminations. The bulbous endings perhaps represent filtration mechanisms, comparable to the glomeruli of the kidney.

In congenital syphilis the cartilage canals are not always affected. They are very frequently affected, however, in particular when the disease becomes well developed during intrauterine life. When affected, they become extremely large, several times their normal size. When one examines with the microscope, one finds that the tissue of the cartilage canal is composed of fibroblasts with rather large nuclei which are oval shaped and that all through the interstices are capillaries distended with red blood cells. We think it probable that the insulation of the blood vessels breaks down in congenital syphilis when the cartilage canals become so vascular and the cartilage cells forming the walls of the

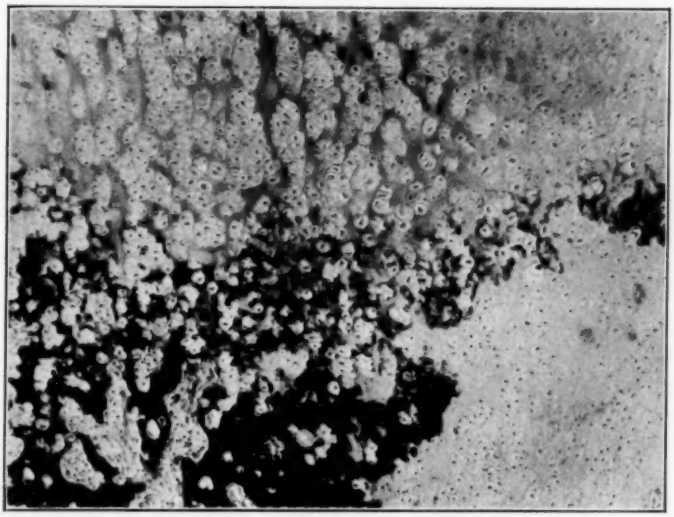


Fig. 5.—Photomicrograph (high power view) from a microscopic section, taken from rib of R. P., No. 1018, aged 4 months. The section shows the extreme degeneration of the cartilage which so often occurs when the disease becomes advanced in fetal life. The cartilage at the right lower corner is badly affected. The cells are small, orderly alignment does not exist, the matrix substance is much increased and there has been failure to take up calcium. At the left, calcification (black) has occurred. But the disorderly pattern of the lattice is enough to show the extreme state of disorder and degeneration, which existed in the cartilage at the time when the lime salts deposited.

tunnels are attacked and destroyed and the tunnels themselves in that way become enlarged. The hypertrophy of the cartilage canal in congenital syphilis is made possible only as the result of destruction of the cartilaginous walls. The descending branches of the cartilage canals which often become enormous, pass through the proliferative cartilage to the shaft as broad channels and meet the vessels of the latter.

Just as the cartilage canals may or may not be attacked by the syphilis, so the proliferative cartilage may or may not be affected. In some cases of severe syphilitic infection the cartilage appears to escape;

in other instances it is attacked and undergoes degenerative change to a degree not seen in rickets, scurvy, or any other disease (Fig. 5). When the cartilage is severely affected, the cells do not develop normally and rapidly undergo degenerative changes. In the severest involvements many of the older cells, those nearest the shaft, seem to be dead. Production of matrix substance seems to be much increased so that in general it seems much more abundant than normal. Large masses of matrix substance appear in the histologic preparations without cells or containing degenerated remains. Column formation of the cells becomes very irregular or stops altogether. The greatest variation in the state of individual cells exists. Some appear swollen and large, while adjacent cells remain as small as osteoblasts. As already indicated, dead and living cells seem to occur close together. The architectural arrangement has gone.

It is thought that the change in the cartilage cells is not a late development, that is, it does not begin in the old cartilage near the cartilage-shaft junction, but has its origin where proliferation begins to take place. In other words, we think that the cells in the generating zone itself must be affected by the disease so that the newly formed cells which are produced are abnormal at the time of their formation. The reason for thinking this is that in typical cases the young cartilage seems abnormal. The family groups appear irregular and distorted and the matrix substance abnormally developed.

When the cartilage is very seriously affected in congenital syphilis, it may not calcify at all or not in the normal way. Either the lymph carrying the inorganic material cannot penetrate or else the cartilaginous material has lost the power to produce the "local factor," phosphatase or some other enzyme, or the pH necessary to give it the property of taking lime salts selectively out of the blood. Large masses of degenerated cartilage remain calcium-free, though lying close to the shaft. One often finds under the microscope that the lime salts deposit only at the margin of the degenerated cartilage, commonly as a continuous layer, or they deposit in the immediate periphery of the cell but not in the matrix substance a short distance away from the cell. In some cases lime salts deposit in the cells themselves, a condition which never happens normally. When the calcification occurs in the cells, the inference seems justified that the cells are dead. Indeed, the very abnormal cartilage in congenital syphilis often calcifies not after the manner of living but of dead tissue.

A proof that the changes which we have described in the cartilage in congenital syphilis are true ones which existed during life and are not artifacts from poor fixation or post-mortem change is furnished by the pattern of the lime salt deposits. If the structure of the cartilage has been abnormal either in rickets, scurvy, or congenital syphilis, the pattern of the lime salt deposits will show it. The depositing lime salts

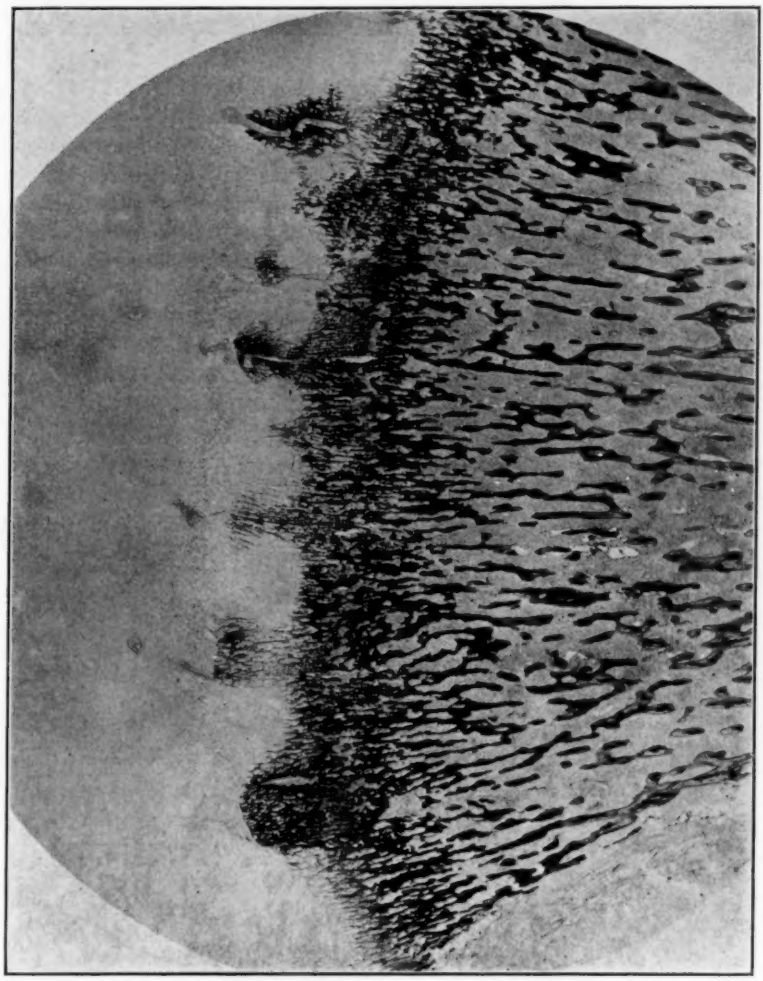


Fig. 6.—Photomicrograph (low power view) of a microscopic section of the lower end of the femur, seen in Fig. 1. It shows plainly the cause of the irregular projections of the end of the shaft into the cartilage. They are due obviously to building up of calcification about the vertical branches of the cartilage canals in advance of elsewhere. The canals are much hypertrophied, as is evidenced by the fact that they show so well at all places in a section in a single plane. The calcified matrix stains black. The network formed by it in toto is the syphilitic lattice. The preparation makes clear that the projections are merely extensions of the lattice.

petrify and perpetuate the pattern of the cartilage. If the formation of matrix substance is irregular or if the matrix substance develops in excess, the pattern of the calcification, i.e., the calcified lattice can be relied upon to tell the tale.

The involvement of the cartilage in any given bone is most irregular, just as the involvement of the cartilage canals is irregular. One may find the proliferative cartilage fairly normal in one place and extremely abnormal in an adjacent one.

We are now prepared to return to our original task and undertake to explain the reason for the irregular extension of the shadows of the end of the shaft into the cartilage, as seen in the x-ray film. Examination under the microscope shows that calcification of the cartilage adjacent to the cartilage canals occurs in advance of calcification of the cartilage between the cartilage canals. The projections from the end of the shaft are nothing more than the extensions of the calcification around the cartilage canals (Fig. 6).

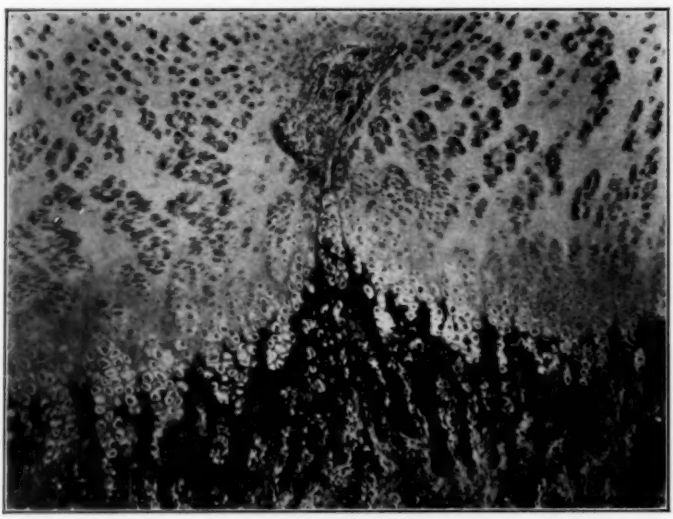


Fig. 7.—Photomicrograph (high power view) of a microscopic section taken from upper end of tibia of Baby C., No. 1110, aged 5 days. This shows that the proliferative cartilage has matured more rapidly around the cartilage canal than at a distance from it. Notice that the clear cells, the cells occupying the regions where calcification is impending, extend high along it. We have explained the extensions of the calcification around the cartilage canals on the ground that the cartilage in proximity to them undergoes the cycle of maturation necessary for calcification at a more rapid rate.

The phenomenon is explained in this way. The cartilage in immediate proximity to the cartilage canals matures much more rapidly than normal and remains more nearly normal in appearance, whereas the cartilage at a distance from the cartilage canals does not or undergoes the degenerative changes described (Fig. 7). The result is that in the

cartilage around the canals calcification occurs faster than normal, whereas between it occurs much more slowly or not at all. The result

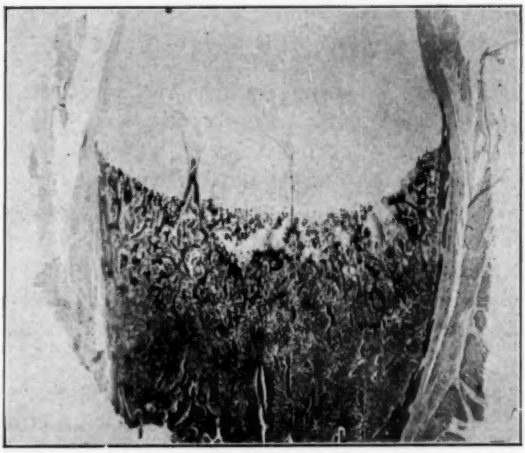


Fig. 8.—Photomicrograph (low power view) of a microscopic section taken from a rib of W. M., No. 1055, aged 9 weeks. It shows metaplastic bone formation in a cartilage canal (the inverted V). Since the formation contains calcium, it casts a shadow and will appear in the x-ray photograph as a projection from the end of the shaft. Metaplastic bone formation in a hypertrophied cartilage canal is a rare sole cause of a projection shadow. Extensions of the syphilitic lattice around the vertical branches of the canals are the common cause. But both conditions may be present in combination.

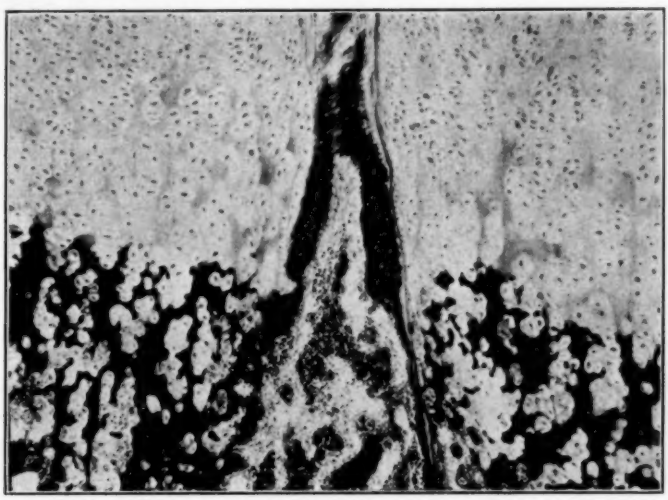


Fig. 9.—Higher power of preceding, showing the metaplastic nature of the inverted V formation in the canal.

is that lattice formation (calcification of the matrix frame) occurs around the cartilage canals in advance of lattice formation between.

The projections are the result, then, of the extensions of the lattice around the cartilage canals and they are rendered even more prominent by the lagging or failure of calcification in the regions between. When one examines the proliferative cartilage through the microscope, one can see that the cartilage around the cartilage canals has not only matured earlier but that the cells have a much more normal appearance than the cells at a distance. The microscope reveals, then, that the generating zone of the proliferative cartilage is not higher placed around the cartilage canals but rather that the cartilage matures in those regions at a greatly increased rate and develops and remains more nearly normal. Under the binocular in the cleared specimen the extensions of the calcification around the cartilage canals appear as mounds or ridges (Fig. 4). These mounds or ridges of calcified material give rise to the characteristic appearance of extensions from the end of the shaft in the x-ray film.

However, another factor may enter into the formation of these projections. It is this. When the branches of the cartilage canals directed toward the shaft become very large in congenital syphilis and the connective tissue contained in them very abundant, it often happens that the connective tissue calcifies and forms metaplastic bone (Figs. 8 and 9). These bands or columns of metaplastic bone, occupying the interior of the canal, are parallel to the long axis of the shaft. They cast shadows and are oftentimes partly, sometimes entirely, responsible for a projecting shadow seen in the x-ray photograph.

In some instances the lattice is built up around all the cartilage canals; in others only around some. The reason for this is not entirely clear.

The description which has just been given explains why the projecting shadows from the end of the shaft have the same consistency in the x-ray film as the end of the shaft itself. The shadow at the end of the shaft is produced by the syphilitic lattice. The projections are nothing more than extensions of the lattice.

The final question is why the cartilage matures more rapidly and calcification occurs higher up around the cartilage canals than elsewhere. We do not have any exact information and are forced to reply in conjecture. It seems altogether probable, however, that the more rapid maturation of the cartilage in the neighborhood of the canals is due to the increased vascularity of the cartilage canals and the breakdown of the normal insulation. In congenital syphilis it is plausible to think that the diffusion mechanism by which the generating zone is supplied with nutrient material becomes disabled. We should suppose that the supply of lymph to the cells immediately adjacent to the canals was increased, so that they matured with an increased rapidity, whereas the cells of the generating zone between received an insufficient or in-

ferior supply and developed more slowly or even underwent degenerative changes. One reason for thinking that this may be the case is the analogous phenomenon observed in rickets and concerned with the phenomenon of cupping. The cells of the proliferative cartilage lying immediately under the perichondrium develop more rapidly than the cells in the interior. The result of the more rapid development of the cartilage cells in the subperiosteal layer is that their destruction and the calcification of the matrix and conversion into shaft occur earlier. Consequently, the shaft forms more rapidly at the extreme periphery than centrally, and cupping develops. The reason which we have assigned for the increased and more rapid maturation of the cartilage cells lying immediately under the perichondrium is that because of their situation they receive under the strain of rickets additional nutrient material from the perichondrial blood vessels.

The question arises whether the condition more responsible for the development of the projections from the end of the shaft in congenital syphilis is the accelerated development of the cartilage around the cartilage canals or the lagging of calcification as the result of the degeneration of the cartilage in the regions between. The reply is that the phenomenon is due primarily to the more rapid maturation of the cartilage around the canals, but that it may be intensified by the failure of calcification of the cartilage between. The reason for this answer is that the phenomenon may occur in congenital syphilis even when the cartilage between the canals does not show much or any degeneration. But under those circumstances the projections are not so well developed.

REMARKS ON A CASE OF CONGENITAL IDIOPATHIC HYPERTROPHY OF THE HEART

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THESE remarks will deal with one of the many subjects upon which the pediatric clinic of the Johns Hopkins Medical School focused study, so-called congenital idiopathic hypertrophy of the heart. Professor John Howland[1] wrote one of the early papers on this condition, his contribution being published in the memorial volumes of 1919, commemorating the seventieth birthday of Sir William Osler. The case report and studies which we shall give demonstrate the important place which, in the past quarter century, chemical techniques have taken in clinical studies, a development fostered by Dr. Howland when he early established a chemical laboratory as an integral part of his department and placed it under the supervision of the late Williams McKim Marriott. Dr. Marriott was ever a dynamic member of the group in the Harriet Lane Home, and his leadership continued to inspire the pediatric department in Baltimore long after he went to St. Louis as Professor of Pediatrics in Washington University.

CASE REPORT

A male baby, aged 8 months, was admitted to the pediatric service of the New Haven Hospital on Dec. 26, 1937, and died the following day, having been in the hospital thirty-two hours (*N. H. H. No. A-77231*).

The family history was noncontributory: there were two pregnancies, the first resulting in a male child now living and well at the age of 19 months; the patient was the product of the second pregnancy.

The patient was born after a normal delivery and weighed 6 pounds 14 ounces. The outstanding feature of the past history was that the child never had thriven; vomiting, coughing, and irritability were the outstanding characterizations given by the parents regarding the patient's ill health. There was never adequate explanation for the vomiting, which varied in occurrence and amount but was often severe. The birth weight was doubled at 7½ months of age and had not increased since. Cough was sometimes present and sometimes absent; it was hacking and nonproductive in nature when present. The symptoms grew worse during the two weeks prior to admission; vomiting and coughing along with alternating drowsiness and irritability became alarming on the day preceding admission. No solid food and only little milk or water were taken. The referring physician diagnosed pneumonia of the left lower lobe.

On admission the patient was observed to be a well-formed child but undernourished (weight, 14.6 pounds and length, 71 cm.). The head was not remark-

From the Departments of Pediatrics and Pathology, Yale University School of Medicine, and the Pediatric and Pathological Services of the New Haven Hospital and Dispensary.

Presented at a joint session of the Johns Hopkins Medical and Surgical Associations, Baltimore, Feb. 26, 1938. The program consisted of contributions by members of the Medical School, Class of 1913.

able. The temperature was normal (37.3° C.), and the child was quiet, slightly cyanotic, but not dyspneic. There was no clubbing of fingers or toes. The significant findings were those relating to the lungs and heart. There was dullness of the percussion note and suppression of breath sounds over the left chest, most marked posteriorly; there were no râles and no bronchial breathing. The heart was enlarged to the right and left of the sternum. The rate was not rapid nor sounds remarkable in intensity; both systolic and diastolic murmurs were heard by a junior observer only. The liver was palpable just below the costal margin, but the spleen was not palpable. The blood pressure was 100/70. The red blood cells were 5,400,000, hemoglobin 13 gm., and white blood cells 6,100, with 42 per cent polymorphonuclears.

A fluoroscopic examination at this time showed a very large heart with variations in density described as a "heart within a heart," findings which suggest pericardial effusion. On the film these differences in density were not easily made out, but the striking enlargement of the heart in all diameters was obvious (Fig. 1). There was some infiltration of the right upper lobe of the lung.

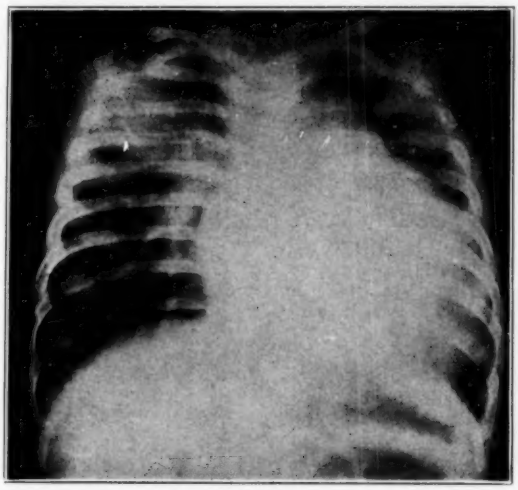

Fig. 1.—Roentgenogram of thorax. Transverse diameter of thorax, 14.7 cm. and of heart, 9.6 cm.; in lateral projection, anteroposterior diameter of heart, 8 cm.

The patient became rapidly and progressively worse. The temperature rose steadily to 40.6° C., and the child became increasingly restless and dyspneic; he seemed to be in very great distress, the cause of which was not obvious. A second white blood count showed 7,100 cells, 48 per cent being polymorphonuclears. Examinations a few hours before death showed signs suggestive of consolidation in the left lower lung posteriorly and right upper lung anteriorly and a heart enlarged in all diameters, extending on the left to the lateral chest wall. The rate was 180 per minute; there were no murmurs, and the sounds were not remarkable. The liver was felt one fingerbreadth below the costal margin in the mid-clavicular line.

An electrocardiogram (Fig. 2) was taken a few hours before death. The rate was 200 and the time interval 0.2 seconds. Dr. Arthur J. Geiger's interpretation was as follows: "The rapid and regular ventricular rate of supraventricular origin is noted. Since no auricular waves are discernible, the tachycardia probably originates in the A-V node. Two aberrant beats, probably of ventricular

origin, were seen in Lead III. The QRS complexes and T-waves are normal. Impression: paroxysmal tachycardia probably of A-V nodal origin.''

The urine showed a slight reduction for sugar, no acetone; the quantity was not sufficient for further study. Blood culture (post-mortem) showed no growth in either blood broth or on blood agar plate. The spinal fluid (post-mortem) contained a few red blood cells; no organisms were seen. The Kahn test was negative.

The clinical diagnosis was congenital idiopathic hypertrophy of the heart; the possibility of glycogen storage disease of the heart, so-called cardiomegalia glycogenica, was suggested.

The autopsy was performed eight hours after death by Dr. Philip LeCompte; the body had been kept in a refrigerator at 32° to 35° F. Only relevant data are presented concerning post-mortem findings.

There was no excess of free fluid in the peritoneal cavity. The anterior edge of the liver extended 2 cm. below the costal margin in the right mid-clavicular line

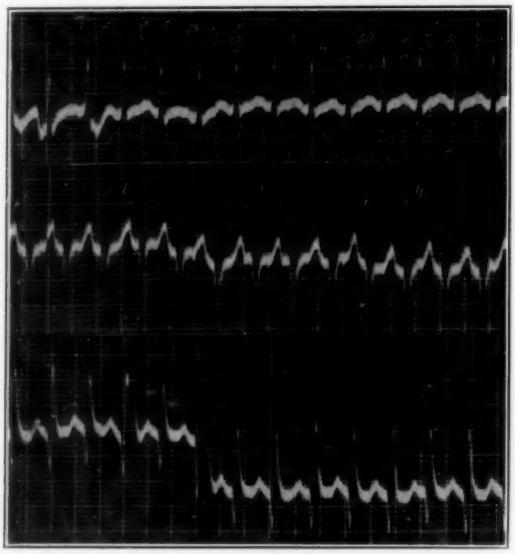

Fig. 2.—Electrocardiogram taken a few hours before death.

and not at all in the left mid-clavicular line. When the chest plate was removed there were found about 20 c.c. of clear straw colored fluid in the right pleural cavity and 2 or 3 c.c. in the left. The striking feature of the appearance of the thoracic cavity was the enormous size of the heart, which occupied most of the left hemithorax and extended well over to the right. The transverse diameter of the heart in situ was 9 cm., while that of the chest was 13 cm. The left lung was markedly compressed and its atelectatic lower lobe lay like a flap over the left side of the heart. Only 3 or 4 c.c. of pale, clear fluid were found in the pericardial sac.

The heart weighed 93 gm., in contrast to 37 gm.,[2] the average for an 8-months-old child. The organ was globoid in shape and appeared to be made up largely of firm, rounded left ventricle. The epicardium was smooth and glistening. No anomalies of the great vessels or valves were present, although special search was made for malformations. The entire aorta and the main branches of the pulmonary artery were carefully examined and did not appear unusual. The coronary vessels

were normal in origin, distribution, and appearance. The right auricle was moderately large, but the walls were not greatly thickened. The cavity of the right ventricle was moderately large, and the walls were 2 to 3 mm. in thickness. The endocardium of the right heart was smooth, thin, and glistening. The left auricle was very large and lined by smooth, glistening endocardium, through which could be seen gray-white opaque material suggesting diffuse fibrous tissue (Fig. 3). The cavity of the left ventricle was very large with flattened trabeculae carneae and

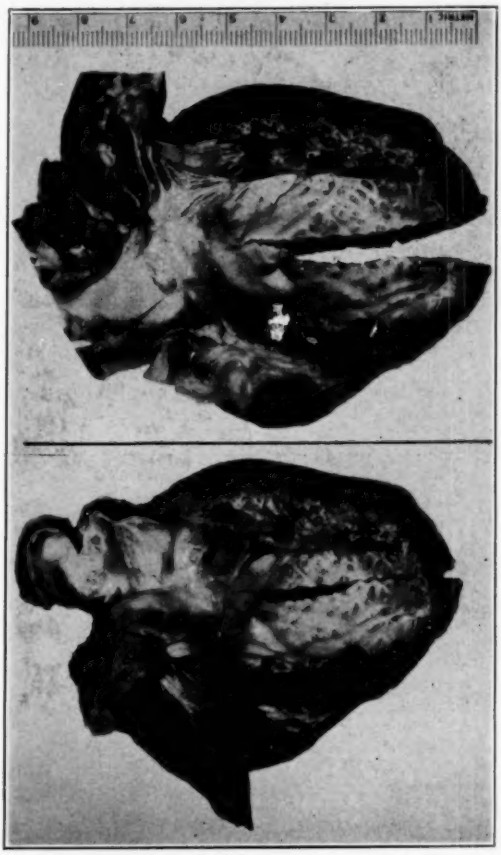

Fig. 3.

Fig. 3.—Left auricle and ventricle showing large chambers, thickened walls, and gray-white, opaque, diffusely thickened endocardium.

Fig. 4.—Left ventricle and aorta showing large chamber, thickened walls. Note absence of narrowing of vessel and gray-white, opaque, diffusely thickened endocardium.

diffuse gray-white, opaque tissue beneath the endocardium like that seen in the left auricle (Fig. 4). The wall of the left ventricle was 8 to 9 mm. thick. On section the muscle was very firm and pale reddish brown with definite yellow-pink areas near the endocardium. The foramen ovale was open to a probe in an oblique manner; the ductus arteriosus was closed.

The upper lobe of the right lung was deeper red than the remainder. On section this portion was mottled with small ill-defined pale yellow-gray areas. The left lung was not remarkable except for complete atelectasis of the lower lobe.

The liver weighed 125 gm. as compared with 254 gm.,[2] the average for an 8-months-old child; the organ was not remarkable except for its relatively small size.

The adrenals (combined weight 2 gm.), the kidneys (combined weight 44 gm.), and the thymus were not noteworthy.

Examination of the brain was not permitted.

Histologic examination of the heart showed a uniform and orderly fibrous thickening without cellular infiltration of the endocardium of the left auricle and

Fig. 5.—Photomicrograph of section of left ventricle showing uniform thickening of subendocardial connective tissue. Elastic as well as collagenous fibers were demonstrated. Note absence of cellular infiltration in both endocardium and myocardium. Hematoxylin-eosin stain was used. (×125.)

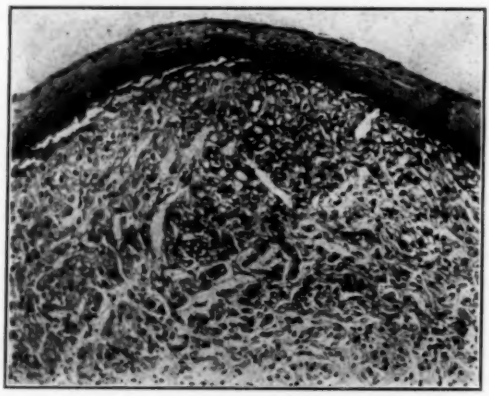

Fig. 6.—Photomicrograph of portion of left ventricle, fixed in absolute alcohol and stained by Best carmine method. Just beneath the thickened endocardium there is a bundle of vacuolated fibers containing black granules (red in original stain). Only in such fibers as these, which are presumably Purkinje fibers, was glycogen demonstrable. Note the absence of granules in surrounding muscle. (×90.)

ventricle (Fig. 5). Elastic fibers were demonstrable in these tissues. There was a questionable slight increase in interstitial fibrous tissue of the myocardium of the right ventricle; there was no cellular infiltration and no scarring of the myocardium. There was no abnormal vacuolization and no fragmentation of the muscle fibers; no

mitotic figures[34] were seen. The diameter of the individual heart fibers did not seem unusual; the average of fifty micrometer measurements of individual fibers gave a value of 9.2 microns as compared with a similar average of 8 microns for the fibers of the heart of average weight of a child of comparable age. The fibers of a heart of average weight of an adult measured 12 microns in diameter.

After fixing the tissues in absolute alcohol, sections of the heart made from both paraffin and celloidin blocks were stained by the Best carmine method for glycogen, and none showed red granules except in a few fibers just beneath the endocardium of the left ventricle, presumably the normal[3] Purkinje fibers (Fig. 6). The stain was checked with saliva-digested controls and tissue known to contain glycogen, as well as by chemical analyses (see Table 1).

Sections of the lungs showed congestion and edema. Sections of the right upper lobe showed in the alveoli many large mononuclear cells with vacuolated cytoplasm. Best carmine stains of tissue from this area showed no glycogen.

Sections of other organs, including adrenals, showed nothing remarkable. Best carmine stains of the liver, skeletal muscle, and kidneys showed no evidence of glycogen, and there was no vacuolization in any organs suggestive of glycogen storage.

Sudan III stains showed no fat in the myocardium or kidneys and only a small amount in the liver cells. In some of the alveoli of the lungs, especially in the right upper lobe, large vacuolated mononuclear phagocytes were seen. The sudan III stain showed that these vacuoles contained fat.

Fresh tissue from the heart, liver, and kidneys was taken at the time of autopsy for chemical analyses for glycogen. Four hours later a piece of the right upper lung was taken from modified Kaiserling solution for similar investigation. The determinations were made according to a modification of the method of Pflüger by Dr. Herman Yannet and showed less than 0.1 per cent of glycogen in heart, liver, kidneys and lung.

COMMENT

The post-mortem study of this case thus demonstrated the presence of an enlarged heart with fibrotic thickening of the endocardium of the left auricle and ventricle. The chemical as well as histologic studies gave no support to a diagnosis of glycogen storage disease of the heart or other organs. The clinical and pathologic findings agreed in supporting the diagnosis of idiopathic hypertrophy of the heart. Presumably, since no hypertrophy of the muscle fibers could be demonstrated, there must have been cardiac hyperplasia to account for the enlargement. Three obvious clinical questions were left unanswered: why was there a sudden unfavorable change in the child's condition a few hours before death? Why did the infant have high fever without leucocytosis? What was the actual immediate cause of death? It might be pointed out here that dramatic exitus is the characteristic termination of patients with congenital idiopathic hypertrophy of the heart.

DISCUSSION

In general it may be said that there are five main cardiac abnormalities with which so-called congenital hypertrophy in infants has been associated when that hypertrophy is not due to malformation or disease of the heart or to extracardiac disorders such as anemia, increased

metabolism, renal disease, or hypertension. The associated conditions referred to are: (1) abnormalities of the great vessels;[4, 5, 32, 45] (2) abnormalities in origin or distribution of the coronary vessels;[6, 47] (3) glycogen storage disease, i.e., von Gierke's disease;[8, 20, 39] (4) rhabdomyoma;[21-23, 42] and (5) myocardial and endocardial "degeneration," atrophy, cellular infiltration, and fibrosis.[4, 5, 24, 45] Fewer cases than formerly are now finally diagnosed as congenital idiopathic hypertrophy because the hearts of many patients so diagnosed clinically fall into one of these five groups and are perhaps not strictly idiopathic. The case we have described showed none of these conditions; there was only cardiac enlargement and endocardial fibrosis which is described in many of the cases diagnosed as congenital idiopathic hypertrophy of the heart and may be an integral part of that disorder rather than a cause of it. Writing in 1936, Mahon[24] states: "Of the sixty-three autopsied cases of so-called 'idiopathic hypertrophy' reported to date, twenty-two have shown, in addition to the cardiac enlargement, endocardial and myocardial changes occurring either singly or in combination, and being the 'simple cardiac defects' most frequently associated with the hypertrophy."

In regard to glycogen disease of the heart there are several cases of cardiac hypertrophy in infants in which this etiology for the hypertrophy has been given.[7-19] It has long been known that in normal animals glycogen promptly disappears from body cells after death. In glycogen storage disease as described by von Gierke and others there are abnormal deposits of glycogen in various organs, notably liver, skeletal muscle, and kidneys, and this glycogen does not disappear promptly after death. Were this not true, probably no description of glycogen disease would have been made, since the first and most of the subsequent studies are based on autopsy examinations made a variable number of hours post mortem; the disorder has been diagnosed also from biopsy material from the liver. No one knows the cause of this failure of normal glycogenolysis; the glycogen itself does not seem to differ from that ordinarily found, and it has seemed obvious to various workers to suggest absence, or failure in some way, of the glycogenase of the organ or blood to function.

Hypertrophy does not always accompany glycogen deposition in the heart. In the 19-month-old patient reported by Unshelm[9] and by Kimmelstiel[18] glycogen was said to be abundant in the heart, yet clinically the organ was not enlarged and post mortem it weighed 50 gm. in comparison with the average for that age of 56 gm.

The emphasis which recent reports in the literature have placed on glycogen disease as an explanation for certain cases of congenital idiopathic cardiac hypertrophy and indeed of focal and diffuse rhabdomyomata has prompted us to report this case. Our purpose in presenting the material is not so much to point out that our patient did not have

glycogen disease chemically or pathologically, but to emphasize the necessity for more comprehensive investigations in the future; all cases of von Gierke's disease should be studied from the cardiologic standpoint, and all cases of idiopathic cardiac hypertrophy should have, if possible, the benefit of the most searching metabolic inquiry. It is not enough, as has been done several times, to restudy the hearts of previously reported cases of idiopathic hypertrophy and state that because of vacuolization of heart muscle fibers or of carmine staining granules in the cells, the essential disorder was glycogen disease of the heart.[6, 8, 13, 14, 25] The tissues for adequate glycogen study must be fixed promptly in absolute alcohol, since glycogen is dissolved, in part, at least, from material which has stood in formalin, leaving empty vacuoles. In our opinion, all of the cases of glycogen disease of the heart which have been comprehensively studied have shown that involvement of the heart was but a part of a general metabolic disorder in which other organs shared, although in some instances possibly to a lesser degree than the heart. Just as the striking clinical symptoms may have pointed to the heart, so the most extensive but not sole pathologic involvement may have been in that organ. The glycogen deposit in von Gierke's disease may be a by-product, so to speak, of disturbances in function of some organ not now identified with the pathology of the disease.[36] For example, in their studies of experimental pituitary basophilism, Thompson and Cushing[37] found that at post mortem dogs which had been injected with gonadotropic extract showed liver cells "highly distended with glycogen. Professor Wolbach states that he has encountered a similar change only in von Gierke's disease. A remarkable change was also apparent in the test animals' *striated muscle,* both cardiac and peripheral. Whereas in the muscle of the control animal the striations are sharply shown, in the test animal they are scarcely distinguishable. Unfortunately no pieces of muscle were fixed in alcohol so that staining for glycogen was precluded."

In contrast to the findings of Dr. Yannet in this case the following data on the glycogen content of organs in other reports are presented for comparison (Table I).

Cardiac rhabdomyoma has been suggested as etiologically responsible for some cases of congenital hypertrophy of the organ. These tumors may be nodular or diffuse and they contain glycogen. They are associated sometimes with tachycardia and arrhythmia and with tuberous sclerosis of the brain. It was natural, therefore, that it should be suggested that diffuse rhabdomyomata of the heart might really be von Gierke's disease of that organ and that glycogen deposits in the brain might account for the associated cerebral disorders. We have a little material bearing on this point. In a patient 9 months of age (N.H.H. No. A-54477), who had multiple nodular cardiac rhabdomyoma and tuberous sclerosis of the brain, a belated, and, therefore, inconclusive

examination of formalin preserved tissue showed in the heart a positive Best carmine stain of the tumor tissue only. There was some carmine staining of the liver cells, but the kidneys and skeletal muscles were negative. Chemical analyses of brain and heart disclosed glycogen content of less than 0.1 per cent. Also, in a recent case of tachycardia in the newborn infant (N.H.H. No. A-76460), in which a small nodule,

TABLE I

GLYCOGEN STUDIES ON PATIENT AND DATA FROM CASES IN THE LITERATURE

	CONGENITAL IDIOPATHIC HYPERTROPHY	HYPERTROPHY OF HEART WITH PATENT INTERVENTRICULAR SEPTUM	GLYCOGEN DISEASE			
	PRESENT CASE	VAN CREVELD[11]	VAN CREVELD[11] (POMPE)	SCHÖNHEIMER[10]	UNSHELM[9]	ANTOPOL[15] ET AL.
Heart	<0.1%	0.55% L.V. 0.05% R.V.	7.96%	-	-	3.57%
Liver	<0.1%	0.103%	9.13%	10.43%	14.2%	3.25%
Muscle	-	0.011%	9.39%	-	-	-
Spleen	-	0.01 %	1.46%	-	-	-
Kidney	<0.1%	0.062%	-	6.53%	-	4.34%
Brain	-	-	-	-	-	-

possibly a rhabdomyoma, was found at the top of the interventricular septum, only small amounts of glycogen and fat were found in focal areas of the myocardium (Best carmine and sudan III stains). Chemical analysis of the heart showed less than 0.1 per cent glycogen.* We believe the subject of cardiac rhabdomyoma is not understood to the satisfaction of all pathologists, but it seems probable, despite the suggestion of Virchow,[21] that while this tumor, whether or not it be a true neoplasm, is associated with certain cases of cardiac disorder, it is not to be very seriously regarded in etiological relationship to the special condition under discussion in this paper.

In respect to the reported lesions in the myocardium of some cases of congenital hypertrophy of the heart, we find ourselves quite perplexed as to their significance. These lesions are usually described by such terms as fibrosis, cellular infiltration, hydropic degeneration.†[13, 25] In our case these changes were looked for in many sections taken from various parts of the heart, including those recommended by Gross.[38] No definite changes, other than the endocardial fibrosis which has been described, were found. Failure to do well, vomiting, coughing, en-

*Analysis by Dr. Yannet in 1938 of the formalin preserved brain of the patient with rhabdomyoma reported by Wegman and Egbert[42] (N.H.H. No. A-32505) showed glycogen content of less than 0.1 per cent.

†Hydropic degeneration is usually described in cases where no attempt was made to demonstrate glycogen at the time of autopsy. It may be that tissue from which glycogen has been dissolved by a formalin solution appears in sections in such manner as to warrant description as hydropic degeneration.

largement of the heart without signs of malformation, dramatic exitus with unexplained fever, and little or no leucocytosis, constitute the usual and characteristic clinical pattern of these cases irrespective of the presence or absence of myocardial lesions post mortem. This causes one to wonder whether the myocardial changes when present are really significant in an immediate etiological sense. In the case reports one sees photomicrographs of myocardial lesions, but from the text it is not always clear whether the pictured lesion is from a small localized area or is representative of widespread damage to the heart. In a limited degree the changes described are common post-mortem findings when carefully searched for in many and various cases in which the question of serious cardiac disease does not arise. It would not seem that these changes, whatever their etiology, could be the cause of the cardiac enlargement or of death in cases of congenital idiopathic hypertrophy.

It is evident that this subject of congenital hypertrophy of the heart in children has been advanced somewhat since the early papers by Howland and others, but many cases classified under this designation are certainly idiopathic. Levy[26] and associates have described similar cases in young adults, and here also the cardiac hypertrophy is unexplained for the most part. Hypertrophy is usually ascribed to increased work[17, 40] which the heart for one reason or another is forced to do. In congenital idiopathic hypertrophy the cause of the increased work is not apparent. One possible cause of "work" hypertrophy in this disorder not yet adequately investigated, however, is arteriovenous fistula or arteriovenous anastomosis.[27, 28, 44] Arteriovenous aneurysms could probably be determined usually by careful physical examination, but anastomoses might be discovered only by means of special methods of vascular visualization. Constriction of the capillary bed is mentioned[46] in some articles without proof of such constriction.

In contrast to the work theory of hypertrophy we should like to call attention to Eyster's extension of the conception of heart injury with dilatation as the etiology of hypertrophy. This theory has recently received favorable clinical appraisal by Davis and Blumgart,[29] particularly in regard to coronary atherosclerosis and congestive heart failure. Eyster produced cardiac dilatation in dogs, in some by means of a constricting band placed for a few days on the aorta, in others by injury of the aortic valves,* and in still others by massive and repeated transfusions. The hearts dilated but soon returned to normal size. However, in about three months they were found to be greatly hypertrophied, a result believed due to the original injury caused by dilatation and stretching. We suggest that something of this nature might have hap-

*It should be pointed out that the operative procedures involved a wider disturbance of structure than just that implied by descriptive statements about obstructive bands and valvular injury. One cannot perform such operations without serious trauma to nerve, cardiac, and other tissue with consequent disturbances of function in addition to those attributed to the principal operative procedure.

pened in some of the patients under consideration.[41] In newborn infants, Dunham and D'Amico[31] showed that the heart is relatively but temporarily enlarged. This enlargement seems adequately explained by postnatal cardiac-respiratory readjustments, but it may be that in some infants the myocardium is damaged in uterine life or in the process of birth and shows subsequent hypertrophy. It is germane to point out that idiopathic hypertrophy of the heart has been described in newborn infants[35] and that most of the cases are described in children less than 1 year of age (forty-one of Kugel and Stoloff's[5] fifty-nine cases were less than 1 year old; the mean age of Abbott's[32] fifteen cases is ten months, the youngest being a newborn infant and the oldest, 4 years of age).

To many physiologists, clinicians, and pathologists the explanation of cardiac hypertrophy is not yet wholly understood.[43] On this subject Sir Thomas Lewis[33] remarked in 1933: "There is still much that remains to be explained; it is clear that there must be hidden sources of increased work or the conclusion that increased work is the cause of hypertrophy needs revision."

Finally, in view of the explanation of some cases of cardiac hypertrophy on the basis of glycogen disease, it is wise to consider that other types of metabolic disturbance might be etiologically operative in certain other cases. The metabolic disorder might be in the cardiac tissue itself, perhaps something to do with chemical changes in contraction; less is known about the physiology of the contraction of heart muscle than of skeletal muscle. Or the stimulus to hypertrophy might arise in other organs or tissues whose functional derangement reacted upon the heart. These are speculations, but in any case it behooves us to go further afield in our search for a solution of congenital idiopathic cardiac hypertrophy than post-mortem studies of the organ itself, valuable as are such investigations.

CONCLUSIONS

A case of idiopathic hypertrophy of the heart in a male child 8 months of age is reported together with pathologic and chemical studies.

Best carmine stains and chemical analyses of tissue from the heart, liver, kidneys, lungs, and striated muscle (no chemical study of the latter) showed no evidences of glycogen storage disease.

The bearing of this case study on the subject of congenital idiopathic hypertrophy of the heart is discussed.

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DIABETES AND PREGNANCY

Observations on the Offspring With a Pathologic Report

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OBSTETRICIANS are not in agreement regarding pregnancy in diabetic women. In the preinsulin era most diabetic women were sterile; now there are numerous reports on diabetes and pregnancy. The apparent frequency with which the pregnancy is complicated by toxemia has led some investigators to a pessimistic outlook (Wiener).[1] Other reports (Peckham)[2] emphasize the successful gestation where a careful diabetic regime is followed. Isolated case studies, such as that of Lawrence,[3] have called attention to improvement in the maternal carbohydrate tolerance after the twenty-eighth week. Lambie,[4] reviewing the whole subject, points out that either aggravation or improvement of the maternal diabetes may take place at any stage of pregnancy. Lambie discusses the possible significance of renal and alimentary glycosurias in relation to temporary diabetes of pregnancy, which has a relatively good prognosis. He advocates induction of premature labor if hyperglycemia has not been controlled, as macrosomia is to be expected. More recently Sherrill[5] has discussed the role of diabetes and pregnancy. Citing the experiments of Carlson and Drennan[6] as well as his clinical experience with diabetes, Sherrill doubts the likelihood of fetal insulin affecting the maternal diabetes.

Since 1922 nineteen infants have been born of women whose pregnancy was considered complicated by diabetes. In fourteen of the mothers glycosuria appeared only with gestation and was controlled by diet or by diet and temporary use of insulin, which suggests glycosuria from causes other than diabetes mellitus. Of the entire group, eleven gave birth to excessively large infants. One mother gave a history of having had nine children: one, by her first marriage, was of normal weight; the other eight, by two subsequent marriages, all weighed 10 pounds or more at birth. Another macrosomic infant was stillborn in the home. The post-mortem changes were so marked that pathologic studies could not be interpreted.

The condition of the newly born infants of diabetic mothers demands special care, not only because of insulin given just before delivery, but also because of the possibility of essential hyperinsulinism as reported by Gray and Feemster.[7] Hence, we have made special studies on those infants born of diabetic mothers in the last few years. Sugar determinations have been made on the blood of the

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CHART I

Mother S.

Aged 21 years
Diabetes for 2½ years
Insulin for 2½ years
Diet: C 110 P 80 F 80
(During most of pregnancy)
Insulin:

Before gestation	– 40 u./24 hr.
6 months gestation	– 30 u./24 hr.
7 months gestation	– 70 u./24 hr.
At term	– 30 u./24 hr.
Post partum	– 30 u./24 hr.

Breast milk:

5/21/1931	– 3.5	per cent sugar
5/25/1931	– 3.1	per cent sugar
6/ 1/1931	– 5.38	per cent sugar

Infant S. (Boy)

Weight at birth 3650 gm.
5/20/1931—Maternal blood sugar: 482 mg. per cent
Infant blood sugar: 244 mg. per cent
5/21/1931—Infant blood sugar: 79 mg. per cent
CO_2 36 vol.
Vomiting repeatedly, clyses of 5 per cent glucose daily for 6 days
5/23/1931—Infant blood sugar: 64 mg. per cent
5/27/1931—Infant blood sugar: 75 mg. per cent
6/11/1931—Infant blood sugar: 89 mg. per cent
Discharged on breast feeding in good condition

11/3/1934

	Blood:	Urine:
Fasting	79.2 mg. per cent	blue
½ hour	108.0 mg. per cent	blue
1 hour	84.6 mg. per cent	blue
2 hour	70.2 mg. per cent	blue
3 hour	75.6 mg. per cent	blue

CHART II

Mother R.

Aged 41 years
Diabetes for 12 years
Insulin for 8 years
Diet: C 170 P 70 F 100
Insulin:

Before gestation	– 30 u./24 hr.
6 months	– 40 u./24 hr.
8 months	– 80 u./24 hr.
Post partum	– 35 u./24 hr.

Infant E. R. (Girl)

Weight at birth 3030 gm.
6/ 8/31—Maternal blood sugar: 155 mg. per cent
Cord blood sugar: 133 mg. per cent
Infant blood sugar: 95 mg. per cent
6/ 9/31—Infant blood sugar: 57 mg. per cent
6/11/31—Infant blood sugar: 82 mg. per cent
Clyses of glucose 3 per cent in Ringer's solution daily for 16 days
6/ 9/31—Cyanotic; vomiting; required Drinker respirator
6/11/31—Vomiting, suggestive of obstruction; fed thickened lactic acid formula
6/25/31—Discharged in good condition

11/19/34

	Blood:	Urine:
Fasting	86.4 mg. per cent	blue
½ hour	140.4 mg. per cent	blue
1 hour	100.4 mg. per cent	blue
2 hour	93.6 mg. per cent	blue
3 hour	82.8 mg. per cent	blue

Reaction

10/17/35

	Blood:	Urine:
Fasting	55 mg. per cent	blue green
½ hour	140.4 mg. per cent	blue
1 hour	178 mg. per cent	
2 hour	142 mg. per cent	blue green
3 hour	135 mg. per cent	blue

mother, the cord, and the infant. The use of 3 per cent glucose in Ringer's solution has been routine when the infant arrived in the nursery. It should be mentioned that the normal newly born infant has an expected blood sugar level lower than that of older infants and children, usually 85 to 100 mg. per cent. Premature infants have even a lower level. The Hagedorn-Jensen capillary sugar determination usually gives values 15 to 20 mg. per cent higher than the macrodetermination (venous blood).

Charts I, II, and III summarize the important features of the three cases studied under the above regime.

CHART III

Mother R.

Aged 42 years
Diabetes for 13 years
Insulin for 9 years
Diet: C 170 P 70 F 100
Insulin:

Before gestation	– 30 u./24 hr.
7 months gestation	– 40 u./24 hr.
7½ months gestation	– 70 u./24 hr.
8 months gestation	– 105 u./24 hr.
Post partum	– 40 u./24 hr.

Infant W. R. (Boy)

Weight at birth (one month premature) 2640 gm.
3/ 8/32—Maternal blood sugar: 87 mg. per cent
Cord blood sugar (micro): 67 mg. per cent
Infant blood sugar (micro): 53 mg. per cent
3/29/32—Infant blood sugar (micro): 72 mg. per cent
3/31/32—Infant blood sugar (micro): 111 mg. per cent
Clyses of glucose 3 per cent given first four days
Blood sugar on 3/31/32 taken after clysis
For shallow breathing on 3/31/32 given CO_2 and O_2

	11/19/34 Blood	Urine:
Fasting	81.0 mg. per cent	blue
½ hour	140.4 mg. per cent	blue
1 hour	75.6 mg. per cent	blue
2 hour	79.2 mg. per cent	blue
3 hour	72.0 mg. per cent	blue

	10/ 5/35 Blood	Urine:
Fasting	73.8 mg. per cent	blue
½ hour	163.8 mg. per cent	blue
1 hour	144.0 mg. per cent	blue
2 hour	84.6 mg. per cent	blue
3 hour	82.8 mg. per cent	blue

The infant's blood sugar, even allowing for the effect of predelivery insulin, may be very low. The cord blood sugar may anticipate this finding by showing a much lower level than that of the maternal blood taken simultaneously. In two of the infants projectile vomiting and cyanosis were striking features, quite possibly related to persistent hypoglycemia. This interpretation circumvented pyloroplasty which was suggested for one of the infants. The use of subcutaneous glucose appeared extremely valuable in carrying the infants through a critical period, after which an apparent adjustment was made.

The following report* concerns the autopsy findings of an infant born of a diabetic mother. During a gestation period of eight months the maternal diabetes was poorly controlled. The report is made because there are complete studies, not only of pancreatic tissue, but also of the other endocrine glands.

CASE REPORT

Family History.—The father, aged 28 years, living and well, and mother, aged 26 years, diabetic, were parents of Baby G., a girl (mother's first pregnancy). There was no family history of diabetes; the mother had eight siblings, living and well.

Present Illness.—Mother had nocturia and polyuria two or three years before discovering she had diabetes. Two and a half years before her pregnancy she was started on a diabetic regime with 40 units of insulin. Reactions caused the dosage to be reduced to 30 units daily. The dosage was 20 units daily for the first seven months of pregnancy, then it was reduced to 10 units a day because of a low fasting blood sugar. Glycosuria necessitated increasing the insulin to 40 units a day at seven and one-half months of pregnancy. One week later vomiting and epigastric pain developed, and at eight months of pregnancy she was hospitalized for treatment of marked acidosis and dehydration.

She continued to vomit in the hospital and it was six days before the acidosis was cleared. Because of cardiac dilatation she was digitalized in preparation for termination of the pregnancy by cesarean section. The infant was delivered without difficulty and after carbon dioxide and oxygen inhalation, had good color for about an hour.

Physical Examination.—Weight 2840 grams; length 48.5 cm. There was marked cyanosis. Respiration was difficult and crying feeble. Heart sounds were normal; lungs atelectatic. Muscles were limp; there was no excessive perspiration and no bulging of fontanels.

Course: Carbon dioxide and oxygen inhalations did not clear the cyanosis. Three hours after delivery the infant was placed in the Drinker respirator and caffeine and continuous inhalations were given. Two and one-half hours later one ounce of breast milk was given by lavage. It was regurgitated with mucus. A change was made to oxygen inhalation despite which the feet and legs became mottled nine hours after delivery. Caffeine and epinephrine were given four times in the next three hours. The infant expired thirteen hours after delivery. A cardiac puncture was done for blood sugar determination immediately after death (value 38 mg. per cent).

Autopsy.—Autopsy was begun six hours and twenty minutes after death. The usual ventral and scalp incisions were made. The organs were normally situated. The umbilical structures were not unusual. Bilateral ovarian cysts protruded above the pelvis into the abdominal cavity. The thymus showed a few punctate asphyxial type subscapular hemorrhages. The heart showed a few petechial subepicardial hemorrhages. The foramen ovale was anatomically open. The ductus arteriosus was widely open. The lungs were unexpanded and showed multiple subpleural petechial extravasations of blood. The thyroid gland was well developed. It was sliced until it revealed a normal appearing parathyroid body. Opening of the gastrointestinal tract revealed meconium from the duodenum downward. The liver revealed recent congestion. The biliary system was patent. Bile was expressed through the cystic and common ducts into the duodenum. The pancreas was situated between the curve of the duodenum and the hilus of the spleen; it was a pink-

*These findings were discussed briefly at the 1934 meeting of the Society for Pediatric Research.

ish-gray color and had the usual cellular consistency. The adrenal glands appeared normal in size, shape, and situation and were heavily coated with white granular fetal-type fat. The inner cortical and central medullary tissue showed a fresh hemorrhagic zone 2 mm. in thickness. The kidneys showed fetal lobulation and were red and congested. The bladder had the usual fetal pointed dome with the urachal top well closed.

The uterus was of the usual newborn infant shape and size. The endometrium appeared blood stained and quite soft. The tubes were draped over large bilateral fluid-filled ovarian cysts resembling Graafian follicle cysts of the adult. In the cyst walls was a plainly visible anastomosing vascular network. The ovary was a polar spongy condensation of tissue which on section was seen to be made up of multiple cysts with rather thick walls.

The meninges were clean and the tentorium cerebelli and supracortical vessels intact. The brain was symmetrical and well formed. The ventricular system appeared normal. The venous sinuses of the skull and the middle ear structures were normal. The pituitary gland was normally situated and was one-fourth or one-fifth the normal size of the adult gland.

The breasts were flat and the nipples barely discernible.

Representative sections were taken for preparation for microscopic examination.

Organ:	*Actual Measurements From Baby G.*	*Standards According to Abt and Grulee**
Thymus	12 gm.	8 to 15 gm., usually 12 gm.
Heart	27 gm. (with aorta)	20 to 25 gm.
Lungs (together)	57 gm.	50 gm.
Liver	135 gm.	120 to 150 gm.
Spleen	9.5 gm.	5 to 20 gm., average 13.5 gm.
Kidneys	28 gm. (together with ureters and bladder)	13 gm. (left), 12 gm. (right)
Brain	440 gm.	220 to 400 gm., average 350 gm.
Adrenals (together)	8 gm.	2 to 16 gm., usually 8 gm.
Pancreas:	4.5 gm.	2.5 gm.
Head	1.5 cm. diameter	1.2 cm. breadth
Tail	0.5 cm. diameter	0.6 cm. thickness
Length	4.0 cm.	5 to 8 cm.
Pituitary	7 by 6 by 4 mm. (one-fourth to one-fifth adult size)	0.1 gm. (one-sixth adult size)
Uterus with tubes and cystic ovaries	30 gm. Left ovary 4.5 by 4 by 3 cm. Right ovary 3.5 by 3 by 2.5 cm.	

*Abt: Pediatrics, W. B. Saunders Co.; Grulee: Clinical Pediatrics, New York, 1926, D. Appleton-Century Co.

Microscopic Description.—The lungs contained congested and unexpanded lung tissue in which fetal plicated bronchioles were empty and clean. There were subpleural petechial, asphyxial type hemorrhages. Interstitia showed no evidence of inflammation.

Heart.—The usual infantile myocardium showed marked interstitial congestion, vacuolated muscle cells; there were scarcely perceptible cross striations.

Liver.—The lobules and cylinders of hepatic cells were well formed and vascular congestion was intense. Immature blood cells were diffusely scattered through the interstitia of the portal channels and along the sinusoids of the lobules. Immature erythrocytic tissue was prominent. Erythroblasts and nucleated erythrocytes were abundant. Giant cells and small groups of myeloblasts and myelocytes were found. Comparison was made with sections of liver from fetuses 11.5 cm. (3.5 months), 15.5 cm. (4 months), 27 cm. (5 months), and five normal term infants. The hemopoietic function was nearest that of the 3.5-month fetus although the lobules

were better developed. The scattered groups of myeloblastic tissue and the eosinophilic granular cells were much more prominent than in any of the sections examined. Except for the number of myeloblastic elements present the picture seemed to be that described in the liver of the third to fifth month.* A search of the literature brings no more recent or different account from this and no reference to its pathologic persistence except in congenital syphilis. MacCallum† describes in the liver in congenital syphilis general retardation of development with the

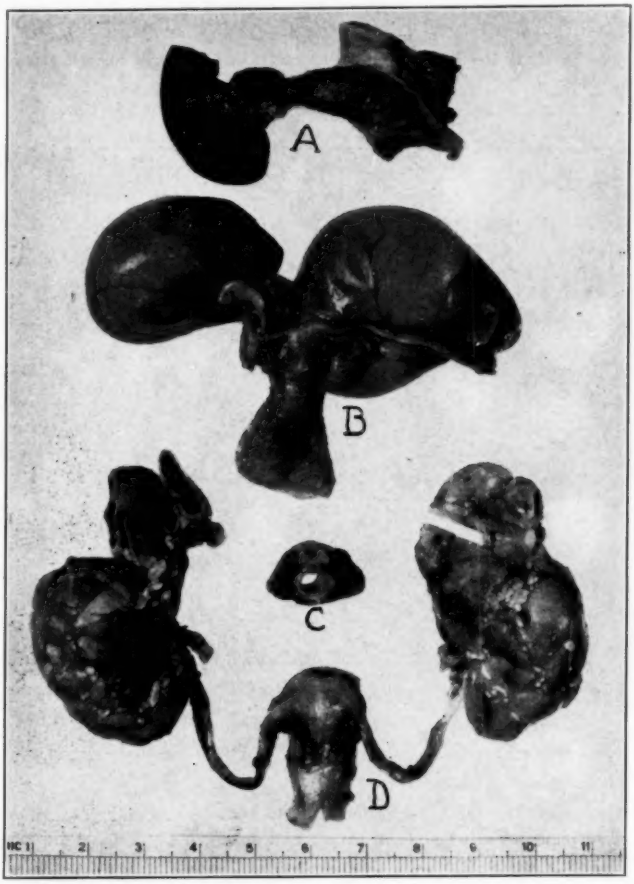

Fig. 1.—Gross appearance of spleen and pancreas. Uterus enlarged; cystic ovaries. *A*, Spleen and pancreas; *B*, uterus and cystic ovaries; *C*, thyroid with tracheal cartilage; *D*, adrenals, kidney, ureters, and bladder.

whole organ engaged in blood formation. This liver was like the ones he describes except there was no fibrosis in the liver or in the bone marrow for which the bone marrow might be compensating, nor was there evidence elsewhere of infection. No spirochetes were found in Levaditi silver-stained sections of the liver. It might

*Kiebel and Mall: Human Embryology, Vol. 2, Philadelphia, 1912, J. B. Lippincott Company.

†Textbook of Pathology, Ed. 3, p. 745, Philadelphia, 1924, W. B. Saunders Company.

be speculated that there was long continued hyperinsulinism in this baby with excess glycogenetic activity and a stimulation for retained hemopoiesis.

Spleen.—The tissue was well formed with normal capsule, trabeculae, vessels, sinusoids, and white and red pulp. There was a normal number of cells of the myeloblastic series in the Malpighian bodies. There was intense recent vascular congestion.

Kidneys.—There was well-formed infantile parenchyma with the usual fetal lobular grouping of glomeruli. No hemopoietic collections of cells were in the interstitia.

Femur.—There was normal fetal bone marrow and well-formed cortical and cancellous bone.

Brain.—Tissue was well formed and without discoverable alteration.

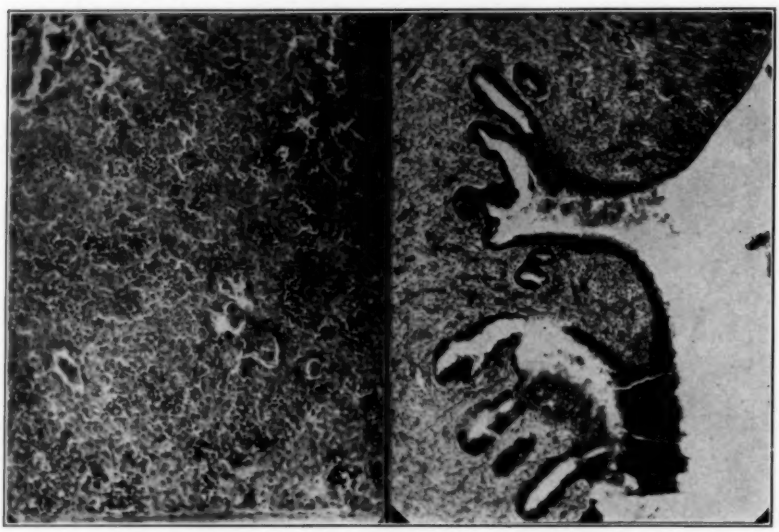

Fig. 2. Fig. 3.

Fig. 2.—Microscopic view of liver showing abundant islands of extramedullary hemopoiesis.

Fig. 3.—Endometrium which is thicker than usual for this age as is the deeper and more complicated endometrial gland formation.

Uterus.—Fetal cervix and infantile myometrium were normal. The endometrium was thicker than in the usual term infant and endometrial glands were deeper and more complicated. The stroma contained many extravasated erythrocytes and a few lymphocytes. A little of the surface epithelium was separating. The picture was that of advanced development. The congestion suggested that of early menstruation.

Placenta and Cord.—The cord showed only the usual physiologic endarteritis. The placenta was free from any inflammatory change except that of endarteritic narrowing of the vessels in the large villous branches. The smaller villi for the most part were quite delicate and well vascularized.

Circulating Blood.—The blood cells studied in the larger vascular spaces in the various organs appeared well formed. In the liver there seemed to be an excessive number of nucleated red blood cells but the average of counts in various organs

placed the relative number at about 1 per cent. There was no disproportion of white to red cells. Polymorphonuclear leucocytes made up about 50 per cent of the white cells.

Pancreas.—Sections from the head, body, and tail of the pancreas all showed a remarkable hyperplasia of the island tissue. In the head region particularly the bulk of the tissue was insular and the islands were not confined but diffuse, often growing about well-formed ducts. Slides stained for reticulum by the silver method used by Otani showed the island cells in places apparently budding from the ducts and having a common basement reticulum. In the head region a capsular membrane seldom was demonstrable about the overgrown island. In the body and tail more discrete islands were present; by comparison with islands in the pancreas of ten normal term infants they were much more numerous and considerably larger. A section from the head region and surrounding tissue showed many normal nerves and lymph nodes and a normal appearing duodenum near the site of the ampulla. The acinous tissue appeared normal.

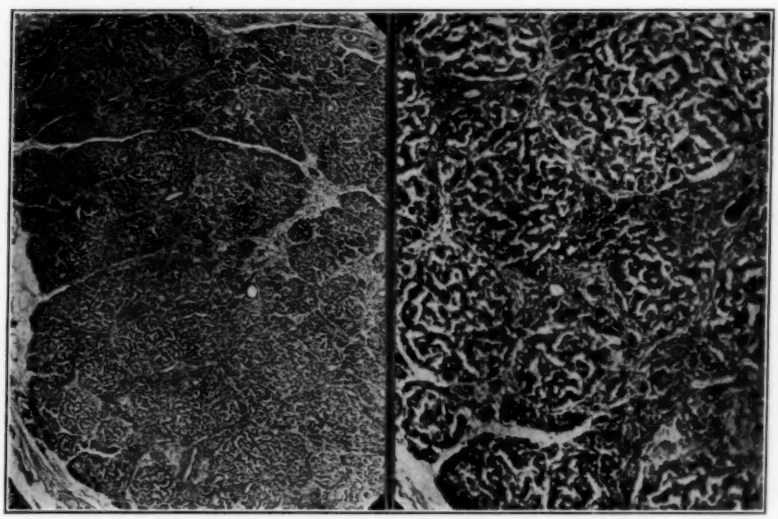

Fig. 4.—Low- and high-power field views of pancreas showing increased number and size of islets of Langerhans.

Gray and Feemster[7] counted and measured the islands in the normal pancreas and in that of an infant of a diabetic mother. They found an average of 184 islands per 50 sq. mm. in sections from all parts of the pancreas in their case and an average of sixty-four islands in six normal cases. In Baby G. the islands of a large part of the head region were not sufficiently delimited to allow counting. Entire lobules appeared as adenomatous formations of island tissue. In many counts from other regions of the head and from the body and tail the average was 196 islands per 50 sq. mm. The count of islands in sections of the pancreas of ten normal term infants (those dying from asphyxia in long labors or from intracranial hemorrhage) agrees remarkably well with that of Gray and Feemster. The average was sixty-two islands per 50 sq. mm. Counts by regions in three of the ten cases were fifty-six for the head, fifty-nine for the body, and seventy-nine for the tail. Gray and Feemster found the average diameter of the islands in

their case to be 213 by 182 microns. The largest island measured 726 by 324 and the smallest 104 by 104. This is in marked contrast to their normal figures of average 115 by 102, largest 206 by 198, and smallest 55 by 50. Islands in the head region of the Baby G. pancreas made up without delimiting reticular membranes practically all of whole lobules measuring up to 3.36 by 4.48 mm. in cross section. The average diameter of the delimited islands was 242 by 190, the largest 880 by 560 microns. As the islands were not followed through serial section the true diameters of the smallest delimited islands could not be determined. In the ten normal sections the average diameter was 114 by 112 and the largest 225 by 192. Gray and Feemster calculated the quantity of island tissue in their case as twenty-four times normal. Disregarding the adenomatous islands in the head of the Baby G. pancreas, by comparison of counted and measured islands the increase in volume was thirty or more times normal.

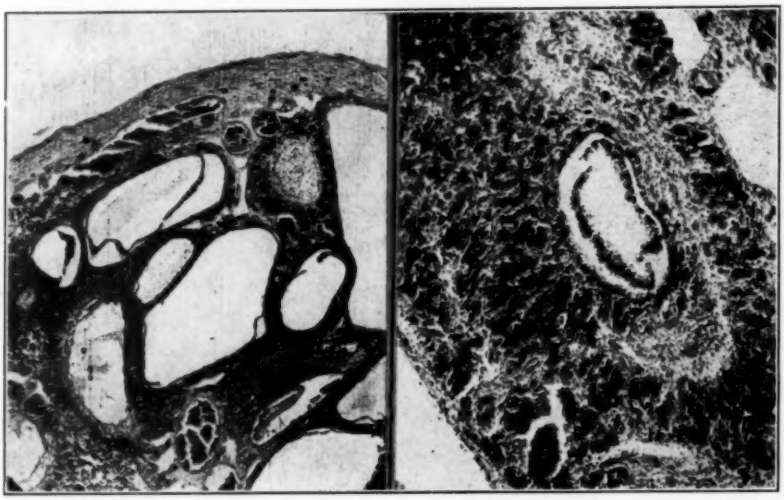

Fig. 5. Fig. 6.

Fig. 5.—Section of ovary showing walls of cysts and interstitial cells.

Fig. 6.—Section of adrenal gland showing wide fascicular zone and scattered medullary cells near central blood vessel.

Otani* describes three types of islands. With silver staining of reticulum to check reticular island capsules, he describes: Type A, islands connected with acini; Type B, with ducts; Type C, entirely separate from exocrine tissue. In reticulum stains by the Otani method 90 per cent of the islands were of Types A and B. More than half were of Type A which perhaps indicates the very embryonal, rapidly growing nature of the islands.

Bloom† advises a Mallory Azan stain to differentiate the island cells. Differentiation in this case has not yet succeeded but studies indicate these islands are mostly A cells.

Ovaries.—The ovarian parenchymal zone was made up largely of large atretic follicles with an intervening stroma filled with large interstitial cells. As compared with sections from ovaries of newborn infants the resting primordial follicles

*Studies on Islands of Langerhans, Am. J. Path. 3: 1, 1927.

†Anat. Rec. 49: 363, 1931.

of the cortex were reduced greatly in number and appeared to be used up in an unusual abortive development which has proceeded en masse. Each atretic follicle has a thin thecal coat, a granulosa layer two or three cells deep, and a degenerate ovum with a pyknotic or fragmented nucleus. These atretic follicles described by Maximov* are found in sparse numbers in the ovary of the newborn infant but are more numerous in the first year of extrauterine life. The thecal cells appear to undergo an abortive lutein change and after the follicular outlines are lost they are found as large polyhedral cells with eosinophilic cytoplasm filling the interstitia. Maximov (p. 655†) states that it is an established fact that the interstitial cells of the ovary in postembryonic life originate from the theca interna of the atretic follicles. The ovaries in this case seem to be an exaggerated illustration of this fact. The larger cystic processes as judged by their wall tissue were abortive follicular cysts.

Breasts.—There was no evidence of undue development or activity in the rudiments of the mammary gland.

In the histologic description of the adrenal, thyroid, parathyroid, thymus, and pituitary glands comparison was made with tissue from term infants. The work of E. R. A. Cooper is used as a reference.†

Adrenal Glands.—The sections showed the usual newly born adrenal gland with a wide fascicular zone. The cortical cell columns became blunt and doubled on the periphery to form a thin, imperfect, glomerular zone. The inner ends of the fascicular columns merged into the boundary zone where they often reached the large vascular channels. The reticular zone was not well separated, though the outer fascicular cells were somewhat more vacuolated. The separate medulla was not present, but scattered medullary cells were seen near the central blood vessels. There were a few large ganglion cells in the same central regions. The inner cortex was extremely vascular.

Cooper points out that the initial sympathochromaffin cells may differentiate into either medullary or ganglion cells and that small numbers of each of the latter cells may be found at birth though no true medulla has separated. Study of sections of natal and postnatal adrenal glands shows the hemorrhagic boundary zone very commonly, the medulla differentiating at about four months, and widely varying numbers of large ganglion cells. The large cells described by Gray and Feemster in the adrenals of the infant born of a diabetic mother probably are ganglion cells. The photomicrograph in their report shows cortical cells of the boundary zone with scattered larger ganglion cells.

Thyroid Gland.—Well-formed tissue made up the well-vascularized interstitia which supported closely packed colloid-containing acini. These acini were small for the most part and lined by cuboidal epithelium. There were many rather dilated acini which approached in size those of the adult gland. The gland in no way differs from Cooper's description of the gland at term except for the dilated, colloid-filled acini. The Baby G. thyroid, compared with term thyroid glands, seemed to have more stored colloid. This may be considered an index of overdevelopment if the gland is considered to have been producing so much colloid it had a surplus to store within acini.

Parathyroid.—The oval body attached to the thyroid capsule at the posteromedian pole of the thyroid was 1 mm. long and 0.4 mm. wide in section. The parenchymal cells were supported by a delicate capsule, trabeculae, and a finer reticulum meshwork. Thin walled capillaries followed the trabeculae. The parenchymal cells formed loosely winding and anastomosing cords. The small round nuclei were the most important feature as the cytoplasm was vacuolated and indefinite in outline.

*Textbook of Histology, p. 650, Philadelphia, 1930, W. B. Saunders Company.

†The Histology of the More Important Human Endocrine Organs at Various Ages, London, 1925, Oxford University Press.

There were scattered chief cells having a finely granular eosinophilic cytoplasm. Judged by Cooper's description the gland was normal.

Thymus.—The cortical and medullary portions were well defined. The Hassall corpuscles were small, separate, and did not reach the periphery. The fibrous septa were not unduly wide. The gland was normal judged by Cooper's description and his quotation of Hammar (Endocrinology, September, 1921).

Pituitary Gland.—The most numerous cells of the anterior lobe were the oxyphils. The cells were grouped about the congested vascular sinuses as in the adult gland. There were a few chromophobe cells on the periphery of the larger cell group. Basophilic cells were very infrequent and showed no tendency toward concentration in any one zone. By comparison with available descriptions the anterior lobe approached the development of a puberty gland. The little posterior and intermediate lobe tissue present appeared quite normal. There was a little less intermediate lobe tissue than would be expected at birth.

Cooper states that undifferentiated nongranular cells are in the majority until the end of fetal life. The oxyphil cells are described at birth as being found gathered in the dorsal and posterior portions of the anterior lobe. The few basophil cells present at birth are at the anterior pole and the anterior part of the ventral margin of the lobe. The neutrophil or chromophobe cells vary greatly in number; they are more numerous than the basophils but tend to be grouped with them. During early postnatal life the epithelial cells of the anterior lobe are well separated from each other and later become closely packed in dense solid masses.

Anatomic and Pathologic Diagnosis.—1. A premature female infant, weight 2835 gm., height 48.5 cm., was estimated to be 9.5 lunar months of age by Haase rule. Lower epiphyseal centers of ossification in the femur were well developed, which places fetal age at over 9 months. There was asphyxia with multiple subpleural, subepicardial and thymus subscapular petechial hemorrhages. Passive congestion of viscera and fetal pulmonary atelectasis were present.

2. There were hypertrophy and hyperplasia of islands of Langerhans.

3. Cystic degeneration of ovaries had occurred and there were large and small abortive Graafian follicle cysts. There was wholesale atresia of follicles with widespread interstitial cell development in the ovaries.

4. Pituitary gland, thyroid gland, and endometrium had relatively advanced development.

5. There was unduly persistent and widespread early fetal type hematopoiesis in the liver. The liver was of normal weight and size for a term infant. The hematopoietic stage was that of a 3.5-month fetus.

DISCUSSION

Some confusion is found in the literature regarding the pathology occasionally seen in infants born of diabetic mothers. Ambard, for example, reported as "congenital diabetes" the case of an infant born of a diabetic mother. His diagnosis was based on finding 1.2 per cent sugar in the infant's urine. Feldman reported the postmortem study of a diabetic woman in the ninth month of pregnancy. The maternal pancreas was definitely atrophic and the bladder urine contained excess sugar and acetone. Microscopic section of the maternal pancreas showed a decrease in island tissue and increased connective tissue. The fetus weighed 3100 gm.; the spleen, liver, adrenals, and kidneys seemed not unusual, and the bladder urine showed excess sugar but not acetone. The fetal pancreas was of normal size

but on microscopic section showed many islets two or four times the normal size, which Feldman interpreted as edematous and associated with an interstitial pancreatitis. In the absence of evidence of syphilis, Feldman concluded that the toxic factor which produced degenerative changes in the maternal pancreas was active in producing changes in the fetal pancreas. The findings then represented an earlier stage of the same process.

The presence of sugar in the bladder of the unborn fetus is admittedly not diagnostic, yet he submits obviously hyperplastic tissue as evidence of diabetes. It is our contention that had the child been delivered hyperinsulinism might have ensued.

Schretter and Nevinny's reports[10] likewise are open to a different interpretation than the one they present. The infant born of a diabetic mother was oversized and had blood sugar of 52 mg. to 62 mg. in the first five days but reached as high as 172 mg. per cent on the sixteenth day. Urinary sugar and acetone determinations were not reported for the infant. The baby died on the thirty-second day with incomplete heart block, which post-mortem examination revealed was probably related to a septal defect of the heart. A later report by the same authors offers more detailed pathology and a valuable comparison with "normal" tissue. "The number of islands were increased over and above the well-recognized increase in the first quarter year of postnatal life. While hypertrophic 'giant islands' occurred only occasionally in the normal control, they dominate the picture in this case." In addition to the pathologic findings in the pancreas there was found an enlarged anterior hypophyseal lobe with an increase in eosinophilic cells. The ovaries were laden with large follicle cysts. The adrenals, although small, showed wide cortices in three cell layers. The thyroid showed poorly developed spaces with but little light staining colloid. Although it is conceivable that during gestation in a diabetic woman there might be initial stimulation of the fetal pancreas and a later "exhaustion phenomenon," the pathological picture must be recognized as distinctly different from that more commonly found in diabetes. In other words, enlargement and hyperplasia usually are evidence of increased function; they may represent depressed function only after an attempted compensation.

The isolation of insulin removed some of the mysteries with regard to the endocrine factors in the maintenance of blood sugar, but the interrelation of pituitary, thyroid, adrenal and liver cannot be denied. (Wauchope[11] and Harris.[12])

The report of Dubreuil and Anderodias[13] recognized hypertrophy and hyperplasia of the insular tissue and postulated a compensatory mechanism. In our own country the study of Gray and Feemster[14] is more convincing. The infant that lived four days had a blood sugar of 67 mg. per cent on the third day. The persistent vomiting which may be considered characteristic of this condition was present.

In addition to hypertrophy and hyperplasia of the insular tissue, there were hypertrophy and hemorrhage of the adrenal glands. Unfortunately no mention is made of other endocrine glands.

Since this last report, Heiberg[15] has published his study of the tissues of an infant born of a diabetic mother. At birth the blood sugar was 88 mg. per cent (method?) but fell to 60 to 70 mg. per cent save for a slight rise after a single clysis of dextrose. The child died on the second day. Island counts showed no increase compared with normal controls, and Heiberg interprets the case as functional hyperinsulinism despite an increase in the size of the pancreas approximately three times that of the control. This latter fact would suggest to us increased function and hypertrophy. The condition of the infant also suggests that perhaps heroic administration of dextrose might have carried the infant over the period of adjustment, such as apparently took place in three of our cases.

With a recent review of the literature, Nothmann and Hermstein[16] discuss the relation of diabetes and pregnancy. In their own case study there was no apparent effect on the maternal diabetes, but in the fetus there were found hypertrophy and hyperplasia of the pancreatic islets.

Correlation of function and pathology is not always easily demonstrable. In diabetes hyalinization, fibrosis and lymphocytic infiltration in the young are found not uncommonly. Hydropic degeneration emphasized by Allen[17] is not frequent in Warren's[18] experience. A few instances of island hypertrophy were found by Warren. Heiberg[19] some years ago reported adenoma of the pancreas in diabetes. Yet we believe such instances are exceptional and that they may relate to extrapancreatic pathology and should not be cited as illustrative pathology.

With regard to the significance of island counts, which Lawrence and McCance[20] chose to disregard, the careful studies of Nakamura[21] are valuable. The latter has shown that in the newborn infant they are normally increased and that definite decrease takes place with age. From a functional point of view we have already mentioned the characteristic low blood sugar of newborn infants, which facts may be related. In the pathology of our fourth case, however, even recognizing the expected increase in number of the islands in infants, the overgrowth of insular tissue, together with the hypoglycemia, leaves little doubt as to correlated hyperplasia and hyperfunction.

Macrosomia of infants born of diabetic mothers mentioned by Dubreuil and Anderodias,[22] and Lambie,[23] suggests that where the maternal hyperglycemia is not controlled an excessively large infant may be expected. (The family cited earlier in our report is striking.)

It will be noted in our report that the cesarean section was performed before term but that by measurements the baby was not premature. This is further corroborated by the skeletal roentgeno-

gram which showed bone growth compatible with 9.5 months' gestation. We may then assume the infant to be relatively macrosomic. The role of glycogen deposition and hypertrophy of tissue has recently attracted attention. In his description of "hepatonephromegali glycogenica," von Gierke[24] postulates a duration of the fetal condition in which the glycolytic ferment is at fault. It is known that glycogen can be accumulated in large amounts in fetal tissue. Van Creveld[25] has suggested this as a basis for hypertrophy of tissues and possibly such conditions as idiopathic hypertrophy of the heart. However, in addition to the overgrowth possibly due to excess glycogen, mention should also be made of the possible endocrine factors. Kraus[26] has emphasized the pluriglandular pathology which he considers secondary to pancreatic insufficiency in diabetes. He found small atrophic adrenals, a small pituitary body, and changes in the thyroid gland. Some change in these endocrine glands might reasonably be expected in essential (pancreatic) hyperinsulinism of the young.

Hydramnios has been reported of frequent occurrence in pregnant diabetic women. Wiener[27] mentions it as an indication for premature induction of labor. It was apparently not an important factor in Peckham's[28] series and there is evidence cited by Lambie[29] that it is related to faulty control of the diabetes. We mention it here, not because of its occurrence in our small series, but because it has been associated with infantile developmental defects.

Sagal[30] has called attention to the frequency of congenital anomalies in children born of diabetic mothers. We were unable to obtain Sagal's article so we do not know whether hydramnios or endocrine factors were blamed for the developmental aberrations.

SUMMARY

There is considerable evidence that under rigid control during pregnancy, the diabetic woman may have a satisfactory course and gestatory product. Although reports vary it is difficult to prove that the infantile insulin production has any effect on the maternal blood sugar. Where the maternal diabetes has not been adequately controlled, the newborn infants may present temporary symptoms referable to hypoglycemia. In some cases these symptoms of cyanosis, vomiting, and feeding difficulty may persist for as long as three weeks and necessitate parenteral glucose administration for that time. A follow-up of one patient showed a hyperinsulin-like sugar curve at 4 years of age.

Reports of postmortem studies of infants born of diabetic mothers vary. In some no hyperplasia of islet tissue has been found, and the hypoglycemia must be considered functional in type. In others the finding of hypertrophy and hyperplasia of the islets of Langerhans makes the correlation obvious.

One study is made in which the relative macrosomia, advanced bone age, and more mature genital tract suggest a pituitary effect. Complete endocrine pathology is reported but with our present limited knowledge the interrelationship is best described as dysfunction. Perhaps some interrelationship will be found to account for the mild as well as the fatal hypoglycemia of the newborn infant. Fetal glycogen storage hypertrophy also is postulated as a possible etiology for some of the pathology.

The authors wish to acknowledge the assistance of the late Dr. Alfred H. Heald, who compiled the pathologic report.

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CONGENITAL HYPERTROPHIC PYLORIC STENOSIS

With Special Reference to Surgical Treatment

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THE question of the treatment of pyloric stenosis is one on which a great deal of discussion still takes place. In England there is, generally speaking, a preference for surgical treatment, but this is by no means universal. A paper published by Svensgaard[1] in 1935, in which treatment with eumydrin is discussed, focused attention once more on the value of medical as opposed to surgical treatment for this condition.

In view of the interest and importance of this subject, it was felt that it would be of value to analyze from a clinical standpoint a series of cases dealt with during the last ten years, keeping in mind especially considerations of treatment and prognosis. The material on which this study is based consists of all patients with pyloric stenosis admitted to the Children's Department of the London Hospital during the period of ten years from Jan. 1, 1928, to Dec. 31, 1937, together with all such patients admitted to the Infants' Hospital, London, under the care of the writer during the time of his association with that hospital, a period of three years. The former group numbers 70, the latter, 32 patients. One other case occurred, with recovery, the diagnosis being confirmed at operation, but, since the case notes have been mislaid and details are not available, it has had to be excluded from the series. During this period there were in addition 2 cases which might be regarded as examples of pylorospasm.

In the matter of diagnosis, rigid criteria were adopted throughout, these being the universally accepted clinical features of the disease, together with the palpation of a pyloric tumor. In 96 patients the tumor was definitely felt, i.e., in 94 per cent of the series; in 2 its detection was doubtful, and in only 4 was it not felt. In each of these six cases where no tumor was definitely felt, the diagnosis was made because of the symptoms being typical and gastric peristalsis being observed, and in each it was confirmed at operation.

Of these 102 patients, 80 of whom were males and 22 females, 4 were treated medically and 98 surgically; 15 died, giving a total mortality rate of 14.7 per cent. In each of the 4 patients treated medically, gastric peristalsis was seen and a pyloric tumor palpated. Three of these recovered, and one died as a result of gastroenteritis; the diagnosis of pyloric stenosis was confirmed at autopsy. As their

From the Children's Department of the London Hospital, and from the Infants' Hospital, Vincent Square, London, England.

number is so small, further detailed comment will not be made on these patients who were treated medically.

The following analysis deals particularly with the 98 patients who were treated surgically. In each of these the diagnosis was confirmed at operation. Treatment was in general conducted on similar lines throughout the series at both hospitals. Many of the infants were given some form of adjuvant preoperative medical treatment, such as a sedative mixture of chloral hydrate and tincture of belladonna before feeding, and, usually for those who were definitely dehydrated, subcutaneous injections of physiologic saline solution; gastric lavage with saline solution was carried out as a routine. Artificially fed infants were usually given a partially skimmed dried milk mixture with added sugar, acidified with lactic acid. In all cases Rammstedt's operation was performed. Many of these infants were given a rectal injection of physiologic saline solution immediately after operation, before receiving any food by mouth, and this was repeated later if necessary. In every case feeding commenced 3 to 4 hours after operation. Small feeds of a glucose solution were given at first, and these were followed by gradually increasing quantities of breast milk or of an artificial feeding mixture similar to that given before operation, the acid being omitted in most cases after a short period. Breast-fed infants were actually sucking from the breast within 27 hours, and those fed artificially were taking an adequate feed within 36 hours of operation.

Of the 98 patients operated upon, 68 were treated at the London Hospital, with 9 deaths, and 30 at the Infants' Hospital, with 5 deaths. When the 98 cases are considered together, there were thus 14 deaths, giving a mortality rate of 14.3 per cent for the patients treated surgically. Four deaths can be regarded as surgical fatalities, and of the remaining ten children who died, seven succumbed to gastroenteritis subsequent to operation. Fifty-three of the operations were performed under general anesthesia, 2 under a combination of general and local anesthesia, and 43 entirely under local anesthesia; 7 deaths occurred subsequently in each of the first and third groups. At the time of admission 17 of the 98 infants were recorded as being less than 4 weeks of age, 69 from 4 to 8 weeks inclusive, and 12 over 8 weeks of age. All those who died were aged 4 weeks or more at the time of admission; 4 of them were 8 weeks or more, one, the oldest of them, being 12 weeks of age.

It is often difficult to be certain, from the history, of the exact duration of symptoms, but, so far as any definite statement seems justifiable, 56 of the patients who recovered may be regarded as having had symptoms for less than 3 weeks prior to admission, and in 7 cases symptoms had been present for 5 weeks or longer. Of those that died six had exhibited symptoms for less than 3 weeks, and 3

for more than 5 weeks. The longest apparently definite duration of symptoms was 8 weeks, in the case of a child who recovered.

Some idea of the general condition of the infants may be conveyed by stating that 57 of the 98 who were operated upon weighed less than at birth when admitted to the hospital; in a few of the remaining 41 infants the birth weight was not recorded. Ten of the 14 who died subsequent to operation are known to have weighed less than their birth weight when admitted to hospital.

Of the 98 infants treated surgically, 34 were breast-fed, 48 were artificially fed, and 16 were fed partly on breast milk and partly on artificial food. It is interesting to note that 12 of the 14 deaths occurred in artificially fed infants, and these included all the cases of gastroenteritis; the 2 breast-fed infants who died fall into the group classed as surgical fatalities. This emphasizes the importance of breast feeding as regards prognosis.

Average figures for length of stay in hospital are purposely not given, as they are likely to convey a totally false impression. The majority were in the hospital for 1 to 3 days before operation; in only 26 cases was operation delayed for more than 3 days after admission. For the 84 surgically treated patients in this series who recovered, the minimum total length of time in the hospital was 6 days, 9 having been in the ward for this short period only. The longest time spent in the ward by any child who recovered was 35 days, this case being complicated by the presence of pyelitis and a rectal abscess. The longest period of hospitalization for any infant in the whole series was 59 days; this particular infant, who died of pneumonia which developed 3 weeks after operation, was actually in the ward for 28 days before operation, owing to the fact that the diagnosis was not established for some time. Thirty infants were in the hospital for less than 10 days, 59 for less than 14 days, and only 25 for a period of 2 weeks or longer. No infant was ever discharged until progress from every standpoint was regarded as satisfactory. As regards the 14 fatalities, 7 infants died within 14 days of admission, and 7 after a longer period in the hospital.

The short time spent in hospital by the majority of these infants treated surgically is in marked contrast to the long periods usually required for medical treatment. Svensgaard,[1] for example, reports having kept her 61 patients treated with eumydrin in hospital for an average period of 77 days, although she admits that they were purposely kept not only until the symptoms had disappeared, but until they had been gaining weight satisfactorily for a long time. In her reported series of patients treated prior to the introduction of eumydrin, the periods of inpatient treatment were even longer. Monrad[2] also gives as average periods of time spent in the hospital 65 and 122 days for breast-fed and artificially fed infants, respectively. In Eck-

stein's paper,[3] in which he contrasts the medical and surgical treatment of patients with pyloric stenosis within the same clinic, he shows that on an average the former required that infants should remain nearly three times as long in hospital as the latter, and his recorded period of time in hospital even after surgical treatment was considerably longer (an average of 34 days, with 13 days as a minimum) than in the series here reported. The question of possibly treating some cases of pyloric stenosis medically as outpatients, must not, however, be overlooked.

Although the advantage of a short period of treatment and early discharge from a hospital ward is unquestioned, the time required for medical treatment would be relatively unimportant if this offered a much better chance of recovery than operative treatment. It is not, however, certain that the case for medical treatment is as yet definitely proved. The evaluation of the comparative advantages of these two main types of treatment is not by any means a simple matter, and critical consideration is necessary in assessing the reports found in the literature.

The differences in the details of treatment adopted by the many physicians working in different clinics naturally introduce variable physical factors. In addition, there is some difficulty in assessing and comparing the results of treatment in the various series of cases that are reported. For example, there is the question of the physical condition of the patients when they are first seen. It will be found that some observers do not record in any detail such data as age and weight of the infants, the duration of their symptoms, and the degree of emaciation at the time of the commencement of treatment. In reporting large series of cases it is admittedly impracticable as a rule to give complete protocols, and average figures are likely to be very misleading, but these comments are made in order to draw attention to a factor which makes for difficulty. The better the condition of a child when he comes under treatment, the better are his chances of recovery, hence the importance, when trying to compare different results, of knowing the duration of the illness and exact details of physical condition. In the absence of complete data it is hardly possible to make a truly critical comparison between the results of different methods of treatment adopted in different reported series. Taking the reports published during the last eleven years by some representative observers, most of whom record a series of not less than 100 patients treated either medically or surgically (the consideration of really small series from this point of view being of little value), it is found that most striking differences occur in mortality rate.

Monrad[2] feels that 24 of his cases should be excluded from the series, as 17 of the patients were moribund and 7 others were suffering from severe complicating conditions such as pyelitis, which made their case

TABLE I

	YEAR OF PUBLICATION	NUMBER OF CASES	MORTALITY
Medical Treatment			
Monrad[2]	1928	223	14.8%
Wolff[4]	1930	92	2.2%
Faxén[5]	1933	126	5.5%
Svensgaard[1]	1935	179	5.5%
Surgical Treatment			
Tisdall, Poole, and Brown[6]	1927	120	13.2%
Haberer[7]	1934	102*	6.9%
Wallace and Wevill[8]	1934	145	24.8%
Thompson and Gaisford[9]	1935	209	14.4%
Jewesbury and Page[10]	1937	303	12.5%
Medical and Surgical Treatment at the Same Clinic			
Eckstein[3]			
Medical cases	1934	92	18.4%
Surgical cases		110	3.4%

*Fifty-eight of these cases are apparently also included in Eckstein's series of 110 surgically-treated patients.

hopeless. If this is done his series is reduced to 199 cases, with a mortality rate of 4.5 per cent. Faxén[5] also thinks that 3 of his patients might well be excluded, as they died of conditions other than pyloric stenosis; he therefore regards his mortality rate as being 3.3 per cent. Such exclusion of cases from these series is not, however, really justifiable, as it would mean that in drawing conclusions from these reports prognosis would be based on the results obtained from the treatment of selected cases.

Eckstein's figures[3] are especially interesting, as they pertain to infants treated in the same clinic, one group by medical and the other by surgical methods; of his reported patients, those submitted to surgical treatment show an outstandingly superior rate of recovery.

Although at first sight it appears from reference to the figures in Table I that the death rate in those treated surgically is on the whole much higher than in those treated medically, certain points should be considered in further detail. Svensgaard,[1] in the paper already mentioned, records a total of 179 patients treated medically. They fall into three groups: 71 cases, with 5 deaths (1911 to 1922); 47 cases, with 3 deaths (1922 to 1927); and 61 cases, with 2 deaths (1927 to 1934). The total mortality, as is shown in Table I, was 5.5 per cent. In the group from 1927 to 1934, however, the mortality was only 3.3 per cent, and if one of the recorded deaths in this group, due to pyelonephritis, is excluded, it is then found that only one child out of 60 died, giving a mortality rate of 1.6 per cent. During each of these three periods referred to, a different method of medical treatment was employed. In the last period, to which Svensgaard[1] draws special attention, eumydrin was prescribed, and in her opinion this was re-

sponsible for the lowering of the mortality rate. Excellent though these results appear to be, it should be borne in mind that consideration of a large series of cases is necessary in order that the treatment of this condition may be viewed in true perspective. Any experienced pediatrician knows that he may have thirty or forty cases without a death occurring, and yet three or four may be lost from the next score or so, although the treatment is similar. On this account it will be necessary to review in the future the results of treatment with eumydrin on a much larger series of patients, before drawing a final conclusion. It may be mentioned here that Braithwaite[11] has just recorded a series of 21 patients treated with eumydrin, 3 of whom died. This might be said to show a mortality rate of no less than 14.3 per cent, but it is of course hardly justifiable to speak of percentages in so small a series.

Furthermore, the question of diagnosis arises, for without a record of very strict criteria it is difficult to be certain that all cases included in any series are actually true examples of congenital hypertrophic pyloric stenosis. In most of the surgically-treated patients in the series quoted, either the diagnostic criteria adopted or the findings at operation appear to put the diagnosis beyond question. Regarding those treated medically, however, it should be noted that Monrad[2] does not consider the palpation of a pyloric tumor to be essential for diagnosis, and Svensgaard[1] does not insist upon it. Faxén[5] does not state his diagnostic criteria at all. It is possible, therefore, that some infants who would be regarded by other observers as suffering from habit vomiting or pylorospasm may be included in such series as these. This would naturally be partly responsible for some of the low mortality rates reported, since these conditions yield readily to medical treatment, which for them is the correct procedure. Wolff's diagnostic criteria[4] appear to be quite rigid and definite. From the fact that only 18 of his patients were treated as inpatients, it might be inferred that the majority of his cases were relatively mild; he states, however, that 56 were severe or very severe. In all probability a factor contributing to the low mortality rate was freedom from the cross-infections which are liable to occur in a hospital ward. From his results it would appear that outpatient treatment by medical methods of, at any rate, the milder cases of pyloric stenosis is worthy of serious consideration, with a view to its more general adoption.

Whether or not pylorospasm, which has already been alluded to, is a clinical entity distinct from pyloric stenosis, is a debatable point. Holt and McIntosh[12] state that a temporary pylorospasm undoubtedly occurs in some young infants, but that the existence of persistent spasm of the pylorus without hypertrophy has still to be proved. They consider that pylorospasm is quite different from hypertrophic pyloric stenosis. Parsons[13] holds that a good case can be made out for the ex-

istence of pylorospasm, and Tisdall, Poole, and Brown[6] believe that the two diseases are clinically distinct and able to be recognized. The writer holds the same view and agrees with these observers that the really important point in differential diagnosis is the palpation of a pyloric tumor. This can be accomplished, as is shown by the series reported in this paper, in about 95 per cent of all cases if careful examination is made, but it is necessary to pay attention to certain points in technique. The observer should sit to the left of the infant, place the whole of his left hand, previously well warmed, on the abdomen, and palpate with the fingers *while the infant is being fed.* If, after examining for about ten minutes, he fails to detect the hard pylorus, which can often be felt to contract and relax under the fingers, it is advisable to try again in the same way during one or more subsequent feeds. In cases of pyloric stenosis, patient repeated examination will almost invariably reveal this physical sign, which should be considered of the greatest importance in making a correct diagnosis. If the tumor cannot be palpated after repeated efforts, the writer feels that a diagnosis of pyloric stenosis can only be justified if the infant, while under careful expert observation, is found to show every other typical symptom and sign. Sometimes the tumor may elude palpation owing to the fact that it is tucked up under the liver. In doubtful cases radiography is often helpful, but it cannot replace physical examination in making a diagnosis. The comments made by Higgins[14] in regard to the pyloric tumor in this condition are of interest and importance to the clinician. He not only lays great stress on the palpation of the tumor, which he regards as decisive in the diagnosis of pyloric stenosis and as the distinguishing feature between this condition and pylorospasm, but he also discusses the development of the hypertrophic process through an evolutionary cycle, resolving in the direction of natural cure. This offers an explanation of the spontaneous recovery which may occur after the age of about three months.

Further factors of importance in assessing the comparative advantages of different methods of treatment are the type of feeding and the length of stay in hospital. Breast-fed infants are known to show a higher recovery rate from pyloric stenosis than those who are artificially fed, and the longer an infant is kept in hospital the greater is the risk of intercurrent infection and resulting death. Early diagnosis and the initiation of treatment while the child is still in good condition has a significant influence upon the prognosis. This is well illustrated by the figures of Tisdall and his co-workers,[6] who point out that, if they excluded from their series those patients admitted to hospital in poor condition, their mortality rate would be reduced to 8 per cent, instead of their stated figure of 13.2 per cent quoted in Table I.

It is not out of place to remark that the surgical treatment discussed in connection with pyloric stenosis usually consists of a combination of

surgical and medical treatment, since such medical procedures as gastric lavage, administration of physiologic saline if the infant is dehydrated, and careful adjustment of the diet, form a most important adjuvant to surgical treatment.

In the light of his experience the present writer considers that pyloric stenosis should not be regarded as a true surgical emergency and that a short period of preliminary medical treatment is desirable in order to counteract, not only dehydration, but also the alkalosis and gastritis which accompany this condition if symptoms have persisted for any length of time. Unless, however, symptoms cease within a day or two, and the infant begins to gain weight satisfactorily, there is a good case for operating at once rather than waiting until the infant, owing to further loss of weight, becomes a bad operative risk. It is important to realize that operation should never be withheld on the grounds of the serious condition of an infant; the worse the condition, the more urgent is the need for early operative intervention. It is in older infants, who are first seen at about 3 months of age and are in relatively good condition, that medical rather than surgical treatment seems especially indicated, since it is generally recognized that after this age the condition is likely to improve spontaneously and eventually to subside of its own accord. Two of the 4 medically treated patients mentioned above were of this age and responded well. Only 2 of those operated upon had reached the age of 3 months on admission, all the others being younger.

The importance of breast feeding in relation to prognosis is generally accepted and is borne out in this series. A further important factor, as already stated, is of course the general condition of the child at the time treatment is commenced; therefore, the earlier the diagnosis is made the better. It must also be emphasized that an infant already suffering from the results of partial starvation should be fed normally as soon as this can be safely accomplished, and the older methods of giving a low diet for a considerable period after operation are unnecessary and not without risk.

The longer an infant remains in hospital the greater is the chance of his acquiring an infection which may prove fatal, and this is particularly the case regarding those fed artificially. In this connection it should be noted that infants suffering from pyloric stenosis who are treated in private practice are found to show a higher recovery rate than those treated in hospital, the lesser risk of cross-infections being an important factor in influencing their course favorably, in addition, naturally, to the advantage of individual nursing. Rapid discharge from a hospital ward is therefore advantageous, and our tendency recently has been to discharge these infants earlier than was usually the case some years ago. From time to time a relatively long stay in hospital is required, as, for example, when there has been delay in ar-

riving at a definite diagnosis, or when the mother's secretion of breast milk is insufficient and it is thought advisable to keep her and the infant in the hospital until an adequate secretion has been established. Our present aim, however, is to discharge the child 5 or 6 days after operation, arranging for the mother to bring him back for the removal of stitches on the ninth day, and subsequently for supervision in the outpatient department as long as this is deemed necessary.

Early diagnosis, a short period of preoperative medical preparation, close cooperation between physician and surgeon (the primary responsibility for the conduct of the case resting with the former) and early discharge from hospital after operation are considered essential if good results are to be obtained. Finally, it should be emphasized that breast feeding has a most favorable influence upon prognosis.

SUMMARY

One hundred and two cases of congenital hypertrophic pyloric stenosis are reported. Ninety-eight of these patients were operated upon, of whom fourteen died, giving a mortality rate of 14.3 per cent.

An analysis of these cases is given, and certain points are commented upon with special reference to treatment and prognosis.

The question of the comparative advantages of surgical and medical treatment of this disease is critically discussed.

It is a pleasure to acknowledge my indebtedness to those of my colleagues who were responsible for the surgical treatment, especially Sir James Walton, who operated on nearly all the London Hospital patients, and Mr. D. Levi, who carried out all the operations on those patients treated by myself at the Infants' Hospital. I wish also to thank Dr. A. G. Maitland-Jones for permission to report such cases as came under his care at the London Hospital.

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SYSTEMATIC HEALTH WORK FOR MOTHER AND CHILD

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HEALTH WORK in early childhood has been developed in Norway, as in nearly all other countries, as isolated infant welfare work, with supervision of the infant throughout the first year. This supervision, performed chiefly by private health organizations in the larger cities, has been an important factor in reducing the infant mortality to the low figures of 39 per 1,000 live births for Norway in the year of 1934 and 44.2 per 1,000 live births in 1935.

Nevertheless, we have various deficiency diseases in this country: in infancy mostly in the form of rickets in the rural districts, up to 43 per cent in the north part of our country, and in later years as dental caries, which affects 99 per cent of our school children.

Furthermore, it is evident from our statistics that our neonatal mortality is relatively high. For Norway as a whole it comprises 50 per cent of the total infant mortality, and for the city of Oslo, with a total infant mortality of 30 per 1,000 in 1935, it accounted for 71 per cent.

From previous work[1] we know that most of the stillborn infants are prematurely born and that the premature infant deaths consititute the greatest percentage of the neonatal deaths.

It has been shown[2] that prematurity may be prevented to a certain extent by a systematic supervision of the mother throughout pregnancy. This is particularly true for unmarried mothers. Supervision in a home for unmarried mothers reduced premature births from 25 per cent in mothers admitted to the home after delivery to 3 per cent in mothers admitted in good time before delivery.

By experimental and clinical work we have found that pregnancy, considered as the essential growth period it is, quite often gives a negative balance as far as certain important nutritional factors are concerned.[3] Out of 27 metabolism experiments performed on 17 women, pregnant from six to nine months, 21 experiments showed a negative calcium balance and 12 a negative phosphorus balance. Furthermore, we found an iron retention below the fetal need in 13 experiments out of 20 performed on 15 women from 25 to 39 weeks pregnant.[4] This negative calcium and phosphorus balance may result, as it is shown by histologic work, in a deficient structure of bones[5] and teeth.[6] It is also found from clinical analysis[7] that the low iron retention may result in a low iron content in the fetal organism, a condition of importance for the development of the infant.

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By regulating the diet of the mothers so that it contains at least 1.6 gm. calcium, 2.2 gm. phosphorus, and 20 mg. iron daily, the balance of these nutritional factors were made positive when the diet was otherwise sufficient. It was also found that the newborn infant's store of vitamins A,[8] C,[9] and D[8] was low in many cases and that this store varied according to the diet and regime of the mother throughout pregnancy.

In the lactating period a negative calcium balance was also found quite frequently, and the vitamin content of the breast milk was found to vary considerably, particularly as to vitamin C. From Gaehtgens' experiments[10] we know the vitamin A content varies also.

Experimentally, as well as clinically, it has been shown that these diet deficiencies during fetal life and early infancy may influence the infants and render them more susceptible to the development of manifest deficiency diseases in postnatal life, as rickets, anemia, tetany, and scurvy, if the postnatal diet as well is insufficient. This is particularly true for premature infants.

These diet deficiencies throughout fetal life and early infancy may be prevented, but only if prophylactic work is started early enough, that is to say, not at the birth of the infant but at the time of conception. This means that a complete prophylactic work in childhood must consist of supervision of the mother throughout the entire period of pregnancy, the following of the infant throughout the first year, and continued supervision throughout the preschool age.

Such a prophylactic health work was planned for the country of Norway two years ago as the only sound basis for the health work in schools, which was started years ago and has spread extensively throughout the country. The whole growth period of the individual will in this way be supervised, and, when the work is well organized, most of the determining factors in general hygiene are thus under control.

Nearly two years ago, September, 1936, this plan was put to work in a rural community just outside Oslo, and it is the preliminary result of this health work since that time which is recorded in the following pages.

The plan worked out by the local physician, Dr. A. Henriksen, in cooperation with Professor Toverud and the author consisted of supervision at a health station throughout pregnancy, once a month in the first seven months, twice during the eighth month and once a week during the ninth month. The infant is likewise examined by the physician once a month during the first half of the first year and every other month during the second half. After the first year the examination is performed three times a year. In addition to this, the teeth are examined and treated from the third year on, in children whose parents have followed the directions of the health station. At the same time intensive propaganda has been carried on in the district for the purpose of making the mothers understand the importance of a proper diet.

When the work was started in September, 1936, we wanted to get an impression of the nutritional state of the population, particularly the state of the pregnant women. For this reason determinations of blood calcium, hemoglobin, ascorbic acid in the blood, and the "distinction power" were performed in all pregnant and in some lactating women.

The methods used in these determinations are the following: for serum calcium, the micromethod described by Nordbö[11] and for hemoglobin, the Zeiss-Ikon colorimeter previously standardized. The mark 100 on this colorimeter corresponds to 100 per cent hemoglobin, or 13.8 gm. per 100 c.c. of blood. For vitamin C in the blood serum we used the methylene blue method of Lund and Lieck[12] based on the principle first described by Martini and Bonsignore, that ascorbic acid can decolorize a methylene blue solution in light. A modification of this method worked out as a micromethod by Elmby and With[13] was used in this work. The "distinction power" was determined according to Edmund,[14] using Tscherning photometric glasses and letters of various gray intensity previously standardized. The so-called long test, blindfolding the eye one-half hour before the performance of the test, was used in this service. The normal dark vision was, according to Edmund and other investigators, considered to be the power of reading at least the first three letters corresponding to the figure of 1.25.

The community in which this work was started has a population of 8,000 inhabitants. From 100 to 120 births a year has been the average figure during recent years in this district. During the twenty months this work has been going on, 117 pregnant women have visited the health center. When examined, the mothers have been given directions as to diet and general hygiene. They have all been told to take 1 tablespoonful of cod liver oil, 1 quart of milk, vegetables, and fruit corresponding to about 75 to 100 mg. of ascorbic acid each day, meat and fish both twice a week, liver and blood at least once a week, besides egg, and whole wheat bread daily. When the hemoglobin was low, iron as ferrichloride was given, and, if milk was not well tolerated, calcium phosphate was added to the diet in an amount calculated to correspond to the calcium content of 1 quart of milk (1.2 gm. calcium).

The nutritional status of these women may be seen from Table I, where the hemoglobin values, calcium content and ascorbic acid content of serum, and the dark vision of these women are recorded. In such determinations the question arises where to put the border line between normal and subnormal values.

As to hemoglobin, the women 15 per cent below the normal figure of 100 per cent, that is, women with a hemoglobin of 85 per cent, and the women 20 per cent below the normal value, that is, women below 80 per cent, have been recorded as subnormal. According to the first calculation, 37, or 31.6 per cent, are subnormal; according to the second calculation, 20, or 17.1 per cent. Repeated determinations were per-

formed in 24 out of these 37 women, and 16 (or 67 per cent) of them returned to the normal value before delivery (Table II).

As far as the "distinction power" is concerned, all previous investigators seem to agree on the figure of 1.25 as the first normal value. From Table I it is seen that 36, or 30.8 per cent, of the women examined showed subnormal values. Thirty-two of these 36 women were followed

TABLE I

THE HEALTH CONDITION OF PREGNANT WOMEN IN THE RURAL COMMUNITY OF SKEDSMO

NO. OF WOMEN EXAMINED	NO. OF WOMEN WITH HEMOGLOBIN BELOW		NO. OF WOMEN WITH DISTINCTION POWER BELOW 1.25	NO. OF WOMEN WITH SERUM CA BELOW		NO. OF WOMEN WITH SERUM ASC. ACID BELOW 0.5 MG. %
	85%	80%		9.5 MG. %	9 MG. %	
117	37 31.6%	20 17.1%	36 30.8%	46 39.3%	18 15.4%	
49						24 49 % 0.3 – 1.2 mg. % lowest and highest figures

TABLE II

PREGNANT WOMEN WITH SUBNORMAL VALUES OF HEMOGLOBIN, DISTINCTION POWER, CALCIUM AND ASCORBIC ACID IN BLOOD SERUM EXAMINED REPEATEDLY DURING PREGNANCY

	NO. OF WOMEN WITH SUBNORMAL VALUE	NO. OF WOMEN REACHING NORMAL VALUE BEFORE DELIVERY
Hemoglobin %	24 (below 85%) 16 (below 80%)	16 (above 85%) 13 (above 80%)
Calcium in serum	36 (below 9.5 mg. %) 16 (below 9.0 mg. %)	31 (above 9.5 mg. %) 25 (10 mg. % or above) 11 (above 9.5 mg. %) 15 (above 9.0 mg. %)
Distinction power	32 (below 1.25)	29 (1.25 or above)
Ascorbic acid in serum	16 (below 0.5 mg. %)	15 (above 0.5 mg. %)

regularly throughout pregnancy, and 29 of them developed a normal "distinction power" during the time of supervision; in only 3 cases did the "distinction power" fail to reach normal before delivery (Table II).

When serum calcium is considered, it is more difficult to fix the limits of normal values. If 9.5 mg. per 100 c.c. of serum is stated as such, 46, or 40 per cent, of the pregnant women were found to have a serum calcium below normal. If only values below 9.0 mg. are noted, 18, or 15.4 per cent, of the women may be considered as having subnormal values. Thirty-six of the 46 women examined were followed with repeated analyses throughout pregnancy; 31 reached values above 9.5 mg. per cent, and in the majority of cases (25) values of 10 mg. per cent and above were found (Table II).

Ascorbic acid in the blood serum was also determined in 49 pregnant women, and values below 0.5 mg. per cent were found in 24, or 49 per cent. Of these 24 women 16 were followed with repeated analyses throughout pregnancy, and all except one reached values above 0.5 mg. per cent. It is not clear where to fix the limit of normal values. Lund has mentioned the value of 0.3 mg. per cent as normal in Denmark. It was found in this series that only women on diets with low vitamin C contents showed similar values, and an increase of the content of the diet to about 75 mg. per day readily raised the content to above 0.5 mg. per cent. All determinations were made three to four hours after breakfast.

Thus we see that evidence of deficiencies in various nutritional factors has been present in 30 to 40 per cent of the pregnant women in this district—deficiencies which in the majority were corrected by diet regulation.

In 147 lactating women "distinction power" was determined, and low values were found in 53 (36 per cent). Thirty-seven of these 53 women were followed with repeated examinations during the lactation period, and 31 of them reached normal values under supervision. Only 6 women remained at the low distinction value of 1.00 (Table III).

TABLE III

"DISTINCTION POWER" IN LACTATING WOMEN

NO. OF WOMEN EXAMINED	NO. OF WOMEN WITH DISTINCTION POWER BELOW 1.25
147	53 (36%) Of these 37 were followed with repeated tests during lactation 31 reached normal values during control

TABLE IV

HEALTH CONDITION OF MOTHER AND CHILD IN THE COMMUNITY OF SKEDSMO

	NO. OF BIRTHS	ECLAMPSIA IN MOTHER	NO. OF STILLBIRTHS	NO. OF PREMATURE BIRTHS
Records from Sept. 1, 1934, to Sept. 1, 1936	219	3 (all died) 1.4%	5 2.3%	11 5%
Records from Sept. 1, 1936 to June 1, 1938 Mothers not visiting the health station	93	2 (alive) 2.2.%	2 2.2%	8 8.6%
Records from Sept. 22, 1936, to June 1, 1938 Mothers visiting the health station regularly	105	0	0	2 1.9%

In order to see what effect this systematic health work has had on the mother and child in this community, we have tried to compare the results achieved at the health station with material from previous years in the same community.

From Table IV it is seen that in the two preceding years, 1934-1936, 3 women out of 219 delivered died of eclampsia. During the last two years 2 out of 93 women who have not visited the health station developed eclampsia. Of the 105 mothers who have been delivered and have visited the health station regularly during pregnancy, not one developed eclampsia, and no stillbirths have occurred. As to the number of premature births 11 infants, or 5 per cent, were born prematurely in the period 1934-1936, and in the period 1936-1938 8 of 93 infants were born prematurely of mothers who had not visited the health center. All had birth weights below 2500 gm. Of 105 mothers attending the center, only 2 were delivered prematurely. One case was a twin birth, and in the other case the infant had a birth weight of 2150 gm. All infants were followed closely and they developed very well.

At this point we may note that the decrease in the number of premature infants as a result of a systematic prenatal control is considered to be of great importance. This fact is illustrated by material from a home for unmarried mothers where the diet and general hygienic control for the last seven years have been raised to meet the actual need during pregnancy as far as we know it today (Table V). Premature birth is a somewhat vague term. The premature infants from this home are therefore classified in three ways. As we see from Table V, a distinct decrease in the number of premature births has taken place in this material, whether it is classified according to the obstetrician's diagnosis, or according to the birth weight (below 2750 gm. or below 2500 gm.). The high incidence of prematurity in these women without prenatal supervision is explained by the fact that we in this home are dealing with unmarried young mothers.

TABLE V

PREMATURE BIRTHS AT SEBBELOW STIFTELSE FROM AUGUST, 1931, TO JUNE, 1938

	TOTAL NO. OF INFANTS BORN	NO. OF INFANTS BORN PREMATURELY ACCORDING TO THE DIAGNOSIS OF THE OBSTETRICIAN	NO. OF INFANTS WITH BIRTH-WEIGHT BELOW 2750 GM.	NO. OF INFANTS WITH BIRTH-WEIGHT BELOW 2500 GM.
Infants born of mothers admitted previous to delivery	224	7 (3.1%)	9 (4%)	5 (2.2%)
Infants born of mothers admitted after delivery or just before	124	33 (26.6%)	30 (24.2%)	19 (15.3%)

From Table VI it will be seen that the incidence of rickets, judged from the examination of infants visiting the center sometime during the first year, was 20 per cent in this district. The diagnosis was made by clinical examinations, and the diagnostic symptoms were craniotabes,

TABLE VI

THE HEALTH CONDITION OF INFANTS IN THE COMMUNITY OF SKEDSMO, SEPTEMBER, 1936, TO JUNE, 1938

	NO. OF INFANTS EXAMINED	NO. OF INFANTS WITH RICKETS
Infants whose mothers were not controlled during pregnancy	152	30 (19.9%)
Infants whose mothers were controlled during pregnancy	105	4 (3.8%) (3 had only an early osteoporotic craniotabes, 1 bowing of the legs)

rachitic rosary, and bowlegs. If roentgenologic studies could be made on these infants, this figure would certainly have been considerably higher. It has also to be mentioned that about one-third of the infants examined were overweight.

Of the group of infants who had been under systematic prenatal as well as postnatal control at the center, 4 showed disturbance in calcification. Temporary and strictly localized craniotabes was observed around the third month in 3 infants. One of these infants was a twin, and another was born in a very poor home where vegetables and fruit could not be provided in sufficient amount. The second and third infants were born of a mother whose prenatal control had only lasted the three last weeks of pregnancy. The fourth infant showed bowlegs at 10 months of age and was suffering from a hereditary adipositas which was so marked that the infant weighed 13.5 kg. at 10 months of age. (Father and grandfather were both very fat.) If we consider the symptoms of the latter group as due to rickets, a lowering in the incidence of rickets had taken place from 19.9 per cent to 3.8 per cent in this district.

We have also been interested in the lactating function of the mothers in this district. We know that inability of many mothers to nurse their infants is a general feature in modern life. The frequency of this inability varies from place to place. It is often said to be unwillingness on the part of the mothers, but this is true certainly in only the minority of cases. All facts today indicate that this inability is a symptom of a deficiency of some unknown nutritional factor or hormone which is the determining one in this process.

The figures in Table VII seem to show that the inability to nurse becomes less frequent when the general hygiene of the mothers is raised. This is even more the case when a closed prophylactic system is in effect. The various health factors, particularly the nutrition of the mother, are then more controlled, with the result that 90 per cent of the unmarried mothers in the last group under the best general hygienic control are able to nurse their infants, as compared with the first group of married mothers in the rural district showing a nursing ability in only 55 per cent.

TABLE VII

		TOTAL NO. OF MOTHERS	NO. OF MOTHERS NURSING THEIR INFANTS EXCLUSIVELY AT LEAST 4 MOS.	PER CENT NURSING ABILITY
Women from Skedsmo without supervision during pregnancy	Open prophylactic system	128	70	54.7
Women from Skedsmo supervised during pregnancy		105	70	66.7
Women admitted to Sebbelow St. after delivery June 1, 1936, to June 1, 1938	Closed prophylactic system	37	27	73.0
Women adm. to Sebbelow St. in good time before delivery June 1, 1936, to June 1, 1938		78	70	89.7

As far as the teeth are concerned, only the children from 2 to 3 years old are recorded; this is the oldest group of children controlled, as the center has been functioning only 21 months. The examinations were performed by Professor Toverud and his assistants at the Children's Department of the Norway Dental School. It is seen from Table VIII

TABLE VIII

THE DENTAL CONDITION IN THE FIRST GROUP OF CHILDREN IN THE COMMUNITY OF SKEDSMO

	NO. OF CHILDREN EXAMINED	NO. OF CHILDREN WITH CARIES	NO. OF CARIOUS TEETH PER CHILD
2 to 3 year old children not belonging to the health station	33	27 (82%)	5
2 to 3 year old children visiting the health station	40	12 (30%)	1.2

that the number of children with carious teeth has decreased from 82 per cent in the group outside the health center to 30 per cent in the children who have visited the center regularly. In this connection it must be mentioned that in regulating the diet, factors influencing the teeth both generally and locally have been heeded, that is, an optimal diet for the mother and infant has been provided. Cod liver oil and orange juice have been given to the infants beginning at 1 month of age, and fruits and vegetables were added at 4 months of age whether breast milk or a cow's milk mixture has been given. After 8 months of age sugar was not given to the infant.

The work described in this paper has been an attempt to see what a systematic health work plan starting at the very first beginning of the

individual with attention to all known nutritional factors is able to secure for the mother and child in a poor rural district. The newer knowledge of nutrition makes us understand that many of the morbid conditions in mother and child are deficiencies, some of them are understood but many of them are not. We certainly do not know yet what is the "normal" nutrition of a pregnant and lactating woman, her optimal need of the various food factors, nor do we know that so far as the child is concerned. Pathologic conditions in teeth, particularly the widespread dental caries, a striking feature in our modern life, proves this. Any attempt, even small, to put out in practical life a systematic prophylaxis may be of interest.

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